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TREATMENT OF ARTHRITIC CONTRACTURES OF THE KNEE

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BOSTON

DEFORMITIES at the knee are among the commonest and most disabling conditions in chronic arthritis, occurring next in frequency to deformities of the hands and feet. Five hundred and eighty-six contractures at the knee (in 313 patients) were found in 1453 patients suffering from chronic arthritis on the wards of the Robert B. Brigham Hospital. A contracture is defined as a relatively fixed shortening of a group of muscles and their ligaments. This shortening develops rapidly within a few weeks. After it has been present for several years, it often leads to irreversible changes in the muscles. The relative frequency of the various types of contractures is given in Table 1. Most of these deformities were

TABLE 1. *Classification of Types of Deformity in 313 Arthritic Patients.*

DEFORMITY	NO. OF CASES	PER CENT
Flexion (more than 10°)		
Simple	504	80.5
With ankylosis of tibia and femur	32	5.1
With subluxation of tibia	19	3.0
With external rotation of tibia	7	1.1
Extension (10° or less of flexion)		
Simple	17	2.8
With ankylosis of tibia and femur	7	1.1
With knees showing no contracture	40	6.4
Total	626	

simple flexion contractures, since this is the usual position that the knee assumes when an inflammation is present[1] (Fig. 1). Flexion contractures of less than 10° were not included in this study because, so far as could be observed, little disturbance in function resulted from such a mild deformity at the knee joint.

Eighty per cent of the cases were uncomplicated flexion contractures. Secondary deformities complicating the flexion contractures were found much less frequently. These, in the order of frequency, were ankylosis of the tibia and femur, subluxation of the tibia on the femur and external rotation of the tibia on the femur. Subluxation of the tibia

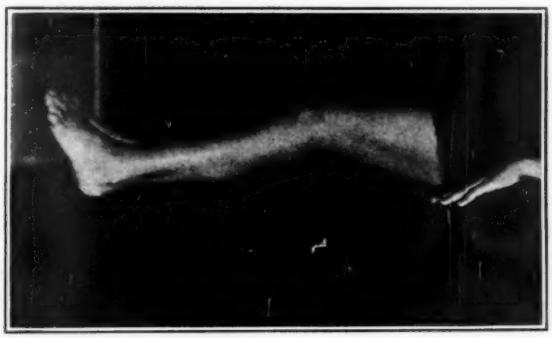

FIGURE 1. *Flexion Contracture of 20° (the usual type of deformity).*

occurred only with partial disintegration of the joint surfaces[2] and with the absence of protection at the back of the knee joint (Fig. 2). External

FIGURE 2. *X-ray Photograph Showing Subluxation of the Tibia on the Femur.*

rotation was usually associated with valgus of the foot and with prolonged muscular spasm in the biceps femoris muscle. Ankylosis of the femur

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and tibia was often the end stage of the arthritis process.[3]

Extension contractures occurred in 2.8 per cent of the knees. These were recorded only if the knee could not be flexed more than 10° from the fully extended position (Fig. 3). This type of contracture was observed only when the knee was kept in extension for long periods during the active stage of the disease,[4] or when much force had been used in the correction of a previous flexion deformity.[5] In 7 cases, the extension contracture was complicated by ankylosis of the tibia and femur.[6]

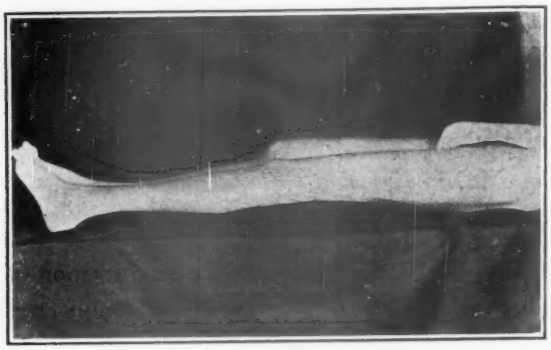

FIGURE 3. *Extension Contracture of Both Knees (about 5° of motion in the right knee, none in the left).*

Involvement of the knee by atrophic arthritis caused all the contractures except 11, which occurred as the result of hypertrophic arthritis. Usually, both knees were similarly involved in the same patient. But there were 40 patients with flexion contracture in one knee and no deformity in the other. The case histories of these patients suggested that local trauma played the major part in this involvement of one knee only.

The deformities that disturbed function to the greatest extent were flexion contractures of more than 30°. Symptoms of sprain soon appeared not only at the knee but also at the hip and foot. Subluxation and external rotation usually increased the symptoms. With flexion contractures of less than 20°, function at the knee was not always disturbed, but weight bearing on these flexed knees tended to increase the deformity. Minimal contractures (less than 10° of flexion) rarely led to significant symptoms unless there was much bony proliferation about the margins of the knee joint. In the mildest contractures, the deformity usually did not change if the arthritis was quiescent.

When the range of motion was greatly restricted in both flexion and extension, or when an ankylosis was present, there was little evidence of sprain at the knee; however, it was usually found in the low back and hip, less commonly at the foot and ankle. Extension contractures rarely produced a strain at the knee, since weight was borne with the knee almost fully straight. But walking led to ache at the hip and ankle because excessive motion was demanded at these joints. Extension deformities were particularly disabling if the patient's work required much flexion of the knee.

To prevent and to correct these contractures of the knee, a program of treatment was evolved that has been modified as more effective methods have been found. In patients seen during the first six months of the arthritis, contractures could usually be prevented. Unfortunately, most of the patients came for treatment only after contractures had developed. The program of treatment and the usual indications are given in Table 2.

TABLE 2. *Program of Treatment of Contractures.*

TREATMENT	INDICATION
Prevention of Contractures	
Avoidance of weight bearing	Pain on walking and articular inflammation
Splinting in full extension	Muscular spasm with tendency to flexion
Exercises	Weakness of muscles
Correction of Flexion Contractures	
Series of plaster casts	Contractures not corrected passively
Pad behind upper end of tibia	Early subluxation
Internal rotation of lower leg in plaster cast	External rotation of tibia
Caliper when standing	Knee too weak to maintain extension on standing
Exercises	Weakness of muscles with no pain on motion
Manipulation	Adhesions limiting motion in one direction only with no inflammation
Posterior capsuloplasty	Resistant flexion contracture with little destruction of articular surfaces
Traction (skeletal)	Flexion or subluxation after operation
Osteotomy	Knee fixed in bad position for weight bearing
Arthroplasty	Stiff joint
Correction of Extension Contractures	
Plaster casts in flexion	Fixation of knee in extension
Lengthening of quadriceps tendon	Resistant extension contractures

The most effective method of preventing contractures at the knee when arthritis was present was rest in full extension until the muscular spasm and pain had subsided. Walking was permitted when motion and weight bearing did not lead to pain. If the period of rest was prolonged beyond two weeks, exercises were often necessary to maintain strength and control of the muscles about the knee. Splinting of the knee in extension was required if there was a persistent tendency to flexion. Fixation was not continued longer than one week without examination of the knee and allowance of a little motion temporarily. Long fixation of the knee without motion tended to produce extensive muscular atrophy and a contracture in extension.

When a flexion contracture could not be corrected passively, an attempt was made to correct

it by a series of plaster casts (Fig. 4). With the fixation of a plaster cast, the muscular spasm usually subsided, and the knee could then be brought into more extension. After two days the plaster cast was cut into an anterior and a posterior half and was removed for short periods to permit the application of heat and for exercises when these could be performed without pain. When 10° or more of correction in the contracture had been obtained, a new cast was applied. Contractures were usually corrected by this method in from one to three months.[7] For persisting weakness of the muscles of the thigh, a caliper was worn when the patient was walking, to maintain correction until the muscles became stronger.

When contractures did not show correction after the use of a plaster cast for several weeks, a manipulation was considered[8] if motion was restricted in one direction only and if there was no evidence of inflammation in the joint. Usually, the most effective method of correction in the resistant contractures was a posterior capsuloplasty, an operation in which the contracted posterior muscles and ligaments are lengthened.[9] When there was much destruction of the articular surfaces and motion was greatly restricted, an osteotomy[10] usually led to a better functional result, with less pain on weight bearing, than a posterior capsuloplasty. Skeletal traction was used only after an operative procedure such as posterior capsuloplasty, particularly for the correction of subluxation of the tibia on the femur.

When there was complete destruction of the articular surfaces, with little or no motion in the joint, an arthroplasty[11] — an operative attempt to form a new joint — was considered if the disease was inactive. Usually, this operation was performed on one knee only, since a certain amount of stability was always lost in the attempt to secure motion. More difficulty was encountered in the cor-

FIGURE 4. *Gradual Correction of Flexion Deformity by Plaster Casts.*

rection of extension contractures than in the treatment of flexion contractures. In the absence of ankylosis, an attempt was made to secure greater motion in flexion by a series of plaster casts holding the knee in flexion. Exercises and the pull of gravity were also employed. When these procedures proved ineffective, a plastic lengthening of the quadriceps tendon[12] was considered.

TABLE 3. *Results of Treatment of Flexion and Extension Contractures.*

TREATMENT	TOTAL NO. OF CASES	GOOD RESULT		FAIR RESULT		POOR RESULT	
		NO. OF CASES	PER CENT	NO. OF CASES	PER CENT	NO. OF CASES	PER CENT
Flexion Contractures							
Series of casts followed by caliper	350	97	28	80	33	173	49
Exercises alone	81	21	26	11	14	49	60
Posterior capsuloplasty	48	19	40	18	37	11	23
Manipulation	44	0	—	16	36	28	64
Arthroplasty	20	2	10	6	30	12	60
Traction (all types)	15	3	20	2	13	10	67
Synovectomy	8	2	25	0	—	6	75
Wedging (forecful)	8	2	25	2	25	4	50
Osteotomy	3	1	33	2	67	0	—
Arthrodesis	1	0	—	1	100	0	—
Extension Contractures							
Casts	15	1	7	3	20	11	73
Exercises	9	2	22	2	22	5	56
Manipulation	4	0	—	1	25	3	75
Lengthening of quadriceps	1	0	—	1	100	0	—
Arthroplasty	1	0	—	1	100	0	—

The types of treatment used and the end results are presented in Table 3. The results of treatment are listed as good with a final result of less than 5° of contracture; fair with from 5 to 15° of contracture remaining; and poor when there was more than 15° of persisting contracture. In flexion contractures, a series of plaster casts was most frequently used. Much better results would have been shown if the contractures had been selected primarily for this treatment. Plaster casts were used in the early treatment of almost all patients. Of the 173 contractures not corrected by plaster casts, 42 were of more than ten years' duration, and 55 had been present over five years. Most of the contractures of long duration and of severe degree required surgical correction later. There is no satisfactory method of determining the resistance of contractures at the first examination. One can usually tell whether plaster casts will be effective only after several weeks of trial. Exercises alone, which were used only for the mildest flexion contractures or as palliative measures, relieved the deformity only when it was of short duration and slight degree. In most cases, exercise failed to prevent an increase in the deformity. It is not considered an effective form of therapy for arthritic contractures, and should be used only in combination with some form of support to the knee.

Posterior capsuloplasty resulted in full correction of the flexion deformity in 40 per cent of the cases. The poor results shown by 23 per cent were due chiefly to failure to maintain correction after the operation was performed. In recent years, full correction of the contracture after the operation has been maintained by skeletal traction or by a plaster cast. Skeletal traction after the manner of Russell[13] was particularly helpful in the correction of severe subluxations of the tibia.

When the patella was bound to the femur by adhesions or by ankylosis, it was necessary to free it to permit full contraction of the rectus femoris muscle (Fig. 5). In three posterior capsuloplasties,

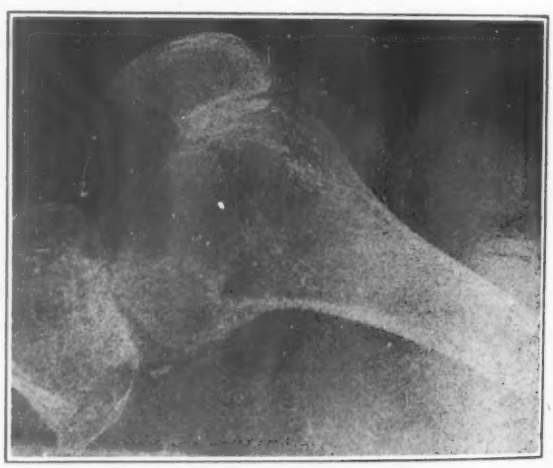

FIGURE 5. *Ankylosis of Patella to Femur.*

the patella was removed, and in three others it was loosened from the femur and then covered with fascia lata. About equally good results were obtained with these methods. No correction of a flexion deformity was maintained when the patella remained fixed to the femur.

The results of manipulation were disappointing. No deformity was fully corrected, and only 36 per

cent were improved. In 4 cases ankylosis in extension occurred after manipulation and in 4 others fracture of the femur occurred during manipulation. Manipulation should be reserved for the correction of contractures of short duration, with limitation of motion in one direction only, in the presence of inactive disease and with no great atrophy of bone or muscle. The only advantage of manipulation is that in selected cases it may release adhesions that cannot be corrected by plaster casts alone.

Arthroplasty for the relief of bony ankylosis at the knee was performed in 20 cases. The poorest results were observed when a great amount of flexion was present before arthroplasty. In such cases, skeletal traction or a series of plaster casts was used to correct the flexion after operation. Arthroplasty was far less effective in chronic arthritis than in ankylosis after trauma or acute infections.

Traction was not an effective method of correcting flexion contractures. Improvement was obtained in only a third of the cases in which it was used. Even skeletal traction was too painful in contractures of long duration to be effective; beneficial results were obtained only after operative procedures in which the contracted muscles and ligaments had been released.

Synovectomy[14] was not used to correct a contracture primarily. At times, it aided the correction of deformity by permitting increased motion at the knee. This operation, planned for the removal of inflamed and thickened tissue from the knee joint, sometimes led to an increased range of motion when motion was hindered by the thickened tissue.

Wedging casts and forceful stretching of the knee with special apparatus were not effective in arthritic contractures. Although correction sometimes resulted in the less resistant contractures, greater stiffness of the knee joint usually followed. In the resistant contractures, pressure sores often developed before much if any correction was obtained.

Osteotomy, a procedure rarely used, led to an improved position for function. This method resulted in no increased motion but gave a better position for weight bearing. Osteotomy, rather than posterior capsuloplasty, was employed when there was little motion in the joint and extensive destruction of the articular surfaces. Usually, an arthroplasty was the operation of choice.

Arthrodesis,[15] although it prevented deformity by eliminating motion at the knee, was not a popular procedure. Only one such operation was performed. Four other patients who had an arthrodesis performed on the knee joint before coming to the hospital stated that they preferred a painful, movable knee to a stiff, painless one. It is a justifiable treatment in chronic arthritis only when there is marked destruction of the joint, with persistent pain on weight bearing, in a patient who must stand at his work.

The treatment of extension contractures has not been encouraging. The results were considered good if the knee could be flexed 60° from full extension, fair if the knee could be flexed 45° to 60° and poor if there was less than 45° flexion. With less than 45°, the patient was unable to climb stairs normally, or to use the leg in rising from a seat. Casts rarely led to an improvement of an extension contracture. Gravity and exercises would be expected to lead to increased flexion, but these were also relatively ineffective. A plastic lengthening of the quadriceps tendon seemed to be the most effective treatment for extension contractures of long duration.

Conclusions

Arthritic contractures at the knee can be prevented by rest, if weight bearing causes pain; by splinting of the knee in full extension, if there is muscular spasm; and by exercise, if there is muscular weakness and atrophy.

When flexion contractures cannot be corrected passively, the best early method of correction is a series of plaster casts, each cast securing as much extension as possible. Calipers and exercises are usually required to maintain full correction until muscular strength is regained.

Flexion contractures too resistant for plaster casts are corrected most easily by a posterior capsuloplasty, which leads to painless weight bearing if the articular surfaces are not destroyed. Manipulation, wedging casts and traction are relatively ineffective procedures. Skeletal traction is of value only after operations that free the contracture and permit extension gradually or after the correction of a subluxation.

Arthroplasty is the procedure of choice in ankylosis if motion is desired, but not in chronic arthritis. Osteotomy is employed when a better position for weight bearing alone is desired.

Plastic lengthening of the quadriceps tendon seems to be the most effective treatment for extension deformities; in general, the treatment of such contractures is not encouraging.

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IMPORTANT CLUES IN CARDIOVASCULAR DIAGNOSIS*

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IT IS of great value in the practice of medicine to keep clearly in mind certain simple diagnostic rules and diligently to seek various important clues to diagnosis. This is particularly true in the study of patients with cardiovascular symptoms or signs. A complete and accurate cardiovascular diagnosis can often be made by the realization of the significance of a single symptom or sign or by a single well-placed question. It is of special interest also that the very multiplicity of symptoms in a nervous person is encouraging evidence of a large nervous as contrasted to an organic cardiac responsibility for illness. The more symptoms, often the less disease.

SYMPTOMS

Pain. Substernal tightness, not often dignified as pain at first, beginning on effort after breakfast on a cold morning in the fall, usually mild the first week or two, and occurring in a business or professional man in the fifties, is, in my experience, the commonest type of onset of angina pectoris due to coronary heart disease. Usually, angina pectoris is a pressure sensation, which is often described by the patient as a difficulty in breathing, and sometimes, therefore, gives rise to an erroneous diagnosis of dyspnea from some cause or other. The patient may say that it is not pain to him, but neither is it true breathlessness. Thus it is important to analyze this symptom in detail. The physician should not use the word "pain" alone in his questioning.

Angina pectoris is often mild, especially at its onset. It does not need to be severe; it may be merely a sensation of slight pressure on some effort that would not normally bring it on. The amount of exercise is more important than the amount of pain. The presence of even mild substernal discomfort on effort is more important than the severity of the pain. The severity of the discomfort or pain is largely dependent on the sensitivity of the person. A sensitive, nervous person will feel the pain more acutely. If slow walking alone brings on mild oppression, this is much more significant than if the pain, no matter how severe, is produced by a faster gait.

Angina pectoris almost invariably occurs at first on effort. If it comes at rest (angina decubitus) one is dealing with an acute coronary occlusion, with or without myocardial infarction. Or else there is some other cause for the pain, perhaps a gastric condition (cardiospasm) or some responsible lesion in the chest other than heart disease.

Meals predispose to angina pectoris on effort, especially breakfast. The patient tends, during the day, to get his second wind, as one might say, and is able to do things after supper or lunch more readily than after breakfast.

Often a patient does not speak of this symptom for days or weeks after it first appears; maybe he does not mention it for years. I have found that especially characteristic of physicians.

The pain tends to be a waxing pain. When the person affected walks a little faster or uphill, the pain grows more and more severe. As a rule, it is a continuous pain until the person stops — continuous, but lasting only a few minutes. It is not a throbbing pain; it is not a sharp pain; it is not a stab; it is not a prolonged ache.

The commonest age at which angina pectoris first appears is the fifties; fifty-two or fifty-three is the average of such patients whom I have seen in the last twenty years. They range, however, from the thirties up to the eighties, but most of them are still active in their work long before retirement. Business or professional men are especially affected; business and professional women may have such symptoms too, but much less commonly. Housewives appear to have angina pectoris less frequently than do business and professional women.

The one most striking etiologic relation of angina pectoris is that of sex. It is preponderantly

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a man's disease. It is essential to remember that women under fifty rarely suffer from true angina pectoris or other manifestations of coronary heart disease, which in the earlier years of life is, as just stated, largely confined to men. The few younger women who do develop it almost always have either hypertension or diabetes mellitus, or else there is a strongly suggestive family history. Those women who have a family history of angina pectoris or coronary heart disease in both branches of the family or in their maternal ancestors alone at young ages, have a tendency to angina pectoris under fifty, even without hypertension; however, this is rare. If a woman is under fifty, chest pain is probably not evidence of heart disease.

Substernal discomfort coming on when seated or recumbent but not on effort is not due to coronary insufficiency; it is most likely of gastric origin, and due to cardiospasm, quite possibly secondary to gastritis from an hiatus hernia. It is vital to distinguish angina pectoris from the heartache over the left breast which is commonly found in other conditions, especially indigestion and nervousness. Tenderness on pressure or palpation over the precordium decreases very much the clinical significance of heart pain, which usually turns out to be only the heartache of neurocirculatory asthenia or pectoral muscle strain.

Another vital point is this: in the presence of prolonged precordial pain, with or without a pericardial friction rub, a definite exacerbation of the pain on deep breathing means acute pleuropericarditis and not coronary thrombosis with myocardial infarction. Misinterpretation in such cases has probably caused frequent errors in diagnosis. Thus, one of the most valuable test questions of all concerns the effect of deep breathing. If in a patient with precordial pain a deep breath increases the pain or perhaps is the chief cause of it, a diagnosis of pleuropericarditis is indicated. The change in the electrocardiogram is atypical and often transient. Cardiologists are now beginning to separate from the large number of patients diagnosed as having coronary thrombosis certain exceptions like the foregoing, with various conditions that may simulate coronary heart disease.

An accurate history will almost invariably enable one to establish the correct cardiac diagnosis. The history is the essential part of the differential diagnosis of heart disease. As already stated pain that comes on when seated or recumbent but not on effort is most likely of gastric origin, and perhaps due to an hiatus hernia. Such pain is often actually improved by standing and walking about; the stomach settles away from the hernia, and there tends to be relief. Belladonna may also give relief, as well as a change in diet, with frequent small meals. One can, of course, have both conditions, — that is, angina pectoris and cardiospasm, — and not uncommonly one may excite the other. It is important to recognize this fact. Many patients with angina pectoris experience relief after belching, but the belching and the cardiospasm associated with it are secondarily induced by the attack of angina, or vice versa. The presence of both conditions adds to the difficulty of the diagnosis, but also to its interest.

Excessively severe chest pain occurring abruptly, — that is, within two or three seconds, — maximum at onset and radiating down the back, in a hypertensive person of middle age or older should suggest dissection of the aortic wall, that is, a dissecting aortic aneurysm. From the coronary-thrombosis group a few patients, as a rule hypertensives, can be picked whose aortic wall has split, usually along the whole length of the aorta and down into the iliacs.

The last point concerning pain has reference to right-upper-quadrant discomfort on effort, due to acute engorgement of the liver, in a patient with mitral stenosis or other cause of right-ventricular strain; this should be viewed with suspicion as an early, probably the earliest, symptom of failure of the right ventricle. Yet, even today, most doctors think of shortness of breath as being the first evidence of heart failure, even in the presence of mitral stenosis. Strictly, this is not true. To be sure, there is a defective mechanism whereby the increased shortness of breath, due to the pulmonary vascular congestion from mitral stenosis, may antedate actual failure. Mitral stenosis acts as a mechanical bar. With tachycardia due to effort, or coming paroxysmally, as in some cases of auricular fibrillation, the right ventricle pumps too much blood into the lungs; this causes congestion of the lungs and shortness of breath. Such dyspnea is due to overaction of the heart, not to heart-muscle failure.

The first symptomatic evidence of right-ventricular failure arises from engorgement of the liver. Naturally, just as the lungs fill up with blood when the left ventricle fails, with dyspnea as the first symptom, so swelling of the liver, with pain, is evidence of failure of the right ventricle. This may come on effort, just as shortness of breath may come on effort, but it is not as yet well recognized. Occasionally this clue is useful. Generally by the time right-heart failure is established, enlargement of the liver has become chronic and no longer painful, but the beginning of the congestion of the liver is painful. This symptom is worth looking for in patients with mitral stenosis who complain of

heaviness or discomfort, especially on effort, in the right upper quadrant of the abdomen. The liver can soak up blood rapidly, and it can also shrink extremely rapidly. I have seen enormous livers subside in forty-eight hours after the beginning of treatment. Thus failure of the right ventricle with a congested liver, like failure of the left ventricle with congested lungs, may subside quickly.

Dyspnea. When the heart is normal in size, dyspnea is not due to heart disease, that is, to either congestive failure of the left ventricle or mitral stenosis, — but most commonly to pulmonary disease or bronchial asthma. When such patients complain of dyspnea, digitalis should not be given. Hence it is extremely important in doubtful cases to determine the size of the heart. When it is normal, dyspnea must be related to other factors. There may be occasional exceptions, — cases of angina with asthmatic reflex, — but they are so rare that they seem to "prove the rule."

In the presence of chronic hypertension of considerable degree, or myocardial infarction, new or old, or aortic valve disease, paroxysmal dyspnea, especially at night, is a bad sign, unless there is paroxysmal tachycardia, auricular fibrillation or severe pulmonary infection or infarction to set it off. It is evidence of acute failure (dilatation) of the left ventricle. Paroxysmal dyspnea has a much better prognosis in mitral stenosis. As stated previously, in mitral stenosis congestion of the lungs is not a sign of muscle failure; it is mechanical. I now have under my care a patient with mitral stenosis who ten years ago nearly succumbed to acute pulmonary edema caused by paroxysmal auricular fibrillation. She developed permanent auricular fibrillation and the heart rate has held ever since at about 70 under digitalis. The patient does not now have dyspnea, and remains in a fair state of health, an impossibility had she had left-ventricular failure as a cause of her pulmonary edema ten years ago. Cheyne–Stokes respiration in a patient when awake means serious circulatory failure. On the other hand, sighing respiration, like precordial tenderness, is a good sign, so far as the heart is concerned. If a patient heaves a deep sigh and says, "Well, here I am at last, Doctor," one knows at once that the diagnosis is chiefly nervous fatigue, and can give, as a rule, a favorable prognosis. But a nervous person who sighs can also have angina pectoris, and nervous people can and do die of angina pectoris or coronary thrombosis.

Periodic dyspnea with tachycardia, collapse and fever, especially at rest, often means pulmonary embolism, particularly in a cardiac patient with congestive failure. This complication is impressive not only because of its importance and frequency, but also because of its neglect. Many persons who are ill in a hospital or at home have unexplained attacks of dyspnea and prostration, and a slight elevation of temperature for a few days. Physical examination may fail to reveal pulmonary infarction, which is often hidden behind other signs; yet almost invariably embolism is responsible for such attacks.

It may be difficult to distinguish between paroxysmal tachycardia and pulmonary embolism. The pulse may go up to 150 or 160 in a few seconds or minutes. One suspects paroxysmal tachycardia, but then finds increased temperature, which is not caused by paroxysmal tachycardia or by heart failure alone — that is, when it amounts to more than half a degree or a degree. Therefore an elevation of two or three degrees of temperature for a few days after an unexplained attack of dyspnea or tachycardia is not to be attributed to either of these conditions. There is likely to be an infarction of the lungs. The embolus comes almost invariably from the legs. One often blames the heart, but in these cardiac cases especially there is a stagnation of blood in the veins of the legs. There may be no sign of phlebitis on physical examination in a good many cases. I have seen three or four of these patients with apparently perfectly normal legs but with proved thrombophlebitis (better called "phlebothrombosis"). There may be an incomplete block of one of the long veins, especially the superficial femoral or long saphenous, which is responsible for the pulmonary embolism that is causing the symptoms. One should be everlastingly on his guard against this complication. It may occur in a person who has never had heart disease. It is to be expected after an injury or an operation, but it is a common medical complaint as well.

One should in such cases always inquire as to possible injury. A recent patient, an elderly man, was suffering a second attack of so-called "pneumonia," which was really a second pulmonary embolism. There had been no operation, and no swelling of the legs was present on examination. On inquiry, it developed that before the first attack of "pneumonia," he was thrown across the room while wrestling, injuring his leg; he had had a temporary swelling of the ankle. Ten days later he had the second attack; the leg was responsible for the pulmonary embolism. Therefore inquiry should always be made as to possible injuries. One can save lives by ligating the responsible veins, when one is quite sure they are responsible. X-ray diodrast venograms, which are now possible, must be taken correctly. Not only is the technic important, but they must be interpreted accurately. Under such conditions they may reveal the correct cause of pulmonary embolism, which may have

been wrongly blamed on the heart. In that event one can tie off the veins on both sides. Lives can be saved by this procedure even more than by giving anticoagulants (such as heparin) after the phlebothrombosis has begun.

Palpitation. Palpitation as a preponderant or isolated symptom generally means an irritable or nervous heart, without structural disease. There need be no serious pain or dyspnea, but a good many nervous persons have every symptom, palpitation, shortness of breath, heartache, fatigue and faintness. The more symptoms, the less significant any one of them is when considered per se. Rarely palpitation does mean heart disease. The majority of long-lived persons throughout the world probably have occasional extrasystoles, of which they may or may not be conscious. Even auricular fibrillation may occur as a minor and isolated functional disorder. In over 100 cases I have seen auricular fibrillation as a relatively unimportant disorder with no other evidence of heart trouble; the hearts of these patients appeared to be structurally sound and essentially normal.

Premature beats, paroxysmal tachycardia and auricular fibrillation and flutter are the arrhythmias that are commonly the cause of palpitation, but still more commonly palpitation is merely an uncomfortable normal rhythm, fast, slow or average in rate.

Tachycardia in abnormal rhythms may explain pain without effort in coronary heart disease, congestive failure in cardiac strain and enlargement from any cause, even in normal infants, dyspnea in mitral stenosis from mechanical blocking of the pulmonary vessels with extra blood, and psychoneurosis, mild or severe, in patients who may become conditioned to any tachycardia. Arrhythmia and tachycardia may simulate coronary insufficiency. When an attack occurs at night, it is important to see the patient during it, or to get an accurate history of the attack. Tachycardia, which is difficult to control by digitalis and rest, particularly in auricular fibrillation, strongly suggests excessive nervousness, thyrotoxicosis, infection or infarction, especially of the lungs. If the heart cannot be adequately controlled in a cardiac patient one of these conditions is indicated.

Faintness and syncope are of more significance alone than when attended by other cardiac symptoms. If a patient faints and has other symptoms, such as palpitation and shortness of breath, neurocirculatory asthenia is the probable explanation.

Signs

With finger-clubbing, cyanosis means serious congenital heart disease, or severe chronic pulmonary disease, or is the result of prolonged residence at altitudes of fifteen thousand feet or more. Cyanosis of high degree is rarely seen in congestive heart failure per se, and so when it appears in such cases, it should suggest a probable complication of pulmonary infarction or infection. Ayerza's disease (that occurring in so-called "black cardiacs") is more a pulmonary than a cardiac disease. The heart may be secondarily affected, with a large right ventricle, but failure of such hearts is seldom seen. The deep cyanosis in such cases is due primarily to the pulmonary disease. Cyanosis should be distinguished from argyria and polycythemia vera. The former occurs predominantly in the cheeks, tongue, ears and nose. Argyria occurs around the eyes and the sides of the nose and mouth. In a congenital cardiac patient, exercise increases the cyanosis, but in argyria it brings out a pinkness that tends to conceal the slate-blue tinge of the skin. Polycythemia gives a deep-red, rather than a purple color.

Jaundice in congestive failure suggests a large lung infarct superimposed on congestion of the liver, which is unable to take care of the blood pigment taken up from the pulmonary infarct.

Cardiac enlargement almost always means permanent heart disease, but there are a few exceptions, with acute and reversible dilatation, as in acute cor pulmonale, acute rheumatic myocarditis, excessive paroxysmal tachycardia, myxedema and some cases of myocardial infarction. One can distinguish preponderant left-ventricular and right-ventricular enlargement best by electrocardiograms, but total enlargement is best detected by x-ray study. A precordial bulge may be due to marked enlargement of the right ventricle.

As to sounds and murmurs, a greatly accentuated pulmonary second sound, especially one greater than the aortic sound, in hypertension means left-ventricular failure. In young persons without murmurs, it usually means congenital auricular septal defect or cor pulmonale; it is the rule in marked mitral stenosis. It is important to listen to the heart sounds. I attended medical school at a time when murmurs were all the rage and not much attention was paid to heart sounds. It was not realized that heart sounds were more significant than murmurs.

Gallop rhythm is almost always a sign of serious dilatation of the ventricles. One should, however, always rule out heart block.

Delicate aortic and mitral diastolic murmurs vary in audibility with body position, the type of stethoscopic chest piece and exercise. They are too often missed. In the interpretation of a continuous murmur, a venous hum in or transmitted from the neck should be ruled out; when that is done, such a murmur over the pulmonary-

valve area is the sign par excellence of patency of the ductus arteriosus.

A harsh systolic murmur at the apex, heard also at the aortic area but not over the lung bases, usually means aortic stenosis; when more blowing in character and heard also at the lung bases but not in the aortic area, a systolic murmur means mitral regurgitation. A systolic thrill palpable over the aortic valve area almost always means aortic stenosis, rarely an aneurysm; at the left border of the sternum it means as a rule a congenital ventricular septal defect.

Left versus right hydrothorax in heart disease is more often due to pulmonary infarction or pleurisy than to congestive heart failure. When hydrothorax is limited to the left side, it is due to some condition other than heart failure, unless the right pleural cavity is obliterated, because fluid usually collects earlier, and more frequently and more copiously in the right pleural cavity than in the left. If you find a limited hydrothorax on the left side, look out for pleurisy, pulmonary infarction or obliteration of the pleura on the right side. Also, look out for polyserositis. All fluid collections are not due to dropsy. There may be inflammation of the type of a polyserositis.

The same statement applies to the finding of rales at the lung bases; that is, pulmonary infection or infarction is the commonest cause of basal lung rales, or even atelectasis may be the cause, and not congestive heart failure.

Engorged neck veins almost always mean right-heart failure, rarely acute or chronic constrictive pericarditis or pressure from a mediastinal tumor, and they practically always mean that the liver is enlarged.

Enlargement of the liver without dilated neck veins and increased venous pressure indicates a noncardiac cause, such as cirrhosis in the early stage, hepatitis or tumor. The position of the liver edge is an unreliable indication of the size of the liver.

Exclusive or preponderant unilateral leg edema means local disease, even in heart failure, provided the effect of gravity — that is, of lying on one side — is ruled out. Often this disease is phlebothrombosis, which may lead to pulmonary embolism.

As to the pulse, a great difference in volume of wrist pulses suggests aortic aneurysm, but pressure from a cervical rib or a tight scalenus anticus muscle on one or the other subclavian artery may be responsible. A well-marked pulsus paradoxus favors acute or chronic constrictive pericarditis, but compression of subclavian arteries on raising the shoulders in deep inspiration should first be excluded. True pulsus alternans means serious left-ventricular weakness, except in cases of excessive paroxysmal tachycardia. Absence of pulse in the feet points oftenest to local occlusive arterial disease or embolism, dissecting aortic aneurysm or coarctation of the aorta. The deep systolic jugular pulse must not be confused with the carotid pulse. It should be recognized that there is a wide range of normal pulse rates in man.

* * *

In conclusion the examiner must everlastingly use his eyes and fingers, his ears and his brain in searching for these simple but important cardiovascular diagnostic clues; in fact, if he is on his toes, he may introduce some new and useful clues himself.

THE USE OF ETHER IN OIL INTRAMUSCULARLY IN THE TREATMENT OF BRONCHIAL ASTHMA

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OLIVER WENDELL HOLMES spoke of his asthma as "the slight ailment that promotes longevity." Unfortunately, however, not all cases of bronchial asthma can be so described. Many cases are characterized by acute symptoms which, though severe, are not prolonged. In others, the asthmatic symptoms not infrequently become chronic and, with the passage of time, not only more intractable but also more severe. Quite often, during an acute episode, some patients pass into a more or less refractory stage during which their symptoms, despite energetic treatment, remain for a variable period constantly acute and relatively uninfluenced.

In the severely acute form, in intractable bronchial asthma (with or without acute seizure) and in status asthmaticus, I have found that the administration of ether in oil intramuscularly has produced gratifying results within a comparatively short time. I have successfully employed this preparation as an adjuvant form of palliative therapy in conjunction with other well-recognized and accepted methods. Its action has always been beneficial.

A report of the results obtained by treating 11 cases of bronchial asthma with intramuscular injections of ether in oil is herein presented. I fully appreciate that although ether in oil intramuscularly as an adjuvant appears to influence beneficially the asthmatic state of this small group of patients, much more clinical investigation is required for a more comprehensive evaluation of its effect.

MATERIAL

Ether in oil† can be obtained commercially in hermetically sealed ampules each containing 2 cc. of a sterile solution of equal parts, by volume, of anesthesia ether and peanut oil.

The administration of ether by injection is neither new nor rare. For years, ether has been classified as a diffusible stimulant[1] and recommended as a hypodermic medicament in its unadulterated state in doses of 15 to 20 minims, repeated in fifteen minutes if necessary.

In 1914, Audrain,[2] in France, introduced the intramuscular injection of ether as an anticonvulsant for the treatment of whooping cough in doses of 1 to 2 cc., repeated daily if required. In 1924, Mason,[3] employing the same technic, was one of the first to introduce this therapy in America. Although the symptoms were favorably influenced, many American investigators thought that the treatment with crude ether hypodermically was not desirable because in a considerable number of cases pain, abscess formation and necrosis developed at the site of the injection. This serious objection was later overcome by diluting the ether with a bland oil (peanut oil) and keeping it aseptic in hermetically sealed ampules. In 1929, Levy and Finkelstein[4] reported the use of this sterile ether in oil solution in 104 cases of whooping cough in which more than six hundred injections were administered without the occurrence of abscess formation or necrosis. The dose employed was 1 cc. of ether in 1 cc. of peanut oil, repeated on alternate days or daily as required. This is the same preparation of ether in oil that I have used for the treatment of bronchial asthma.

APPARENT MODE OF ACTION

There is ample evidence that ether, in some manner not as yet fully understood, has a modifying pharmacologic action on the asthmatic symptoms. According to Rackemann,[5] ether in experimental anaphylaxis modifies anaphylactic shock so that the animal survives a dose of antigen that would otherwise be fatal. Vaughan[6] states that asthmatic patients often experience relief for variable periods following surgery. This fact is well recognized by many allergists. Ether anesthesia was deliberately induced by Kahn[7] in 4 patients with intractable asthma. They were temporarily relieved, but not for so long as sometimes happens after surgery. Since its introduction by Maytum,[8] ether in oil by rectum for the relief of severe asthma has been well received by a number of investigators.

These facts have led to the intramuscular administration of ether in oil as an adjuvant for the treatment of severe bronchial asthma. Despite the fact that this method has had a limited employment, the results are so constant that an apparent mode of action may be rationalized.

Although the ether is mixed with peanut oil, the latter does not prevent the immediate diffusion of the ether because patients can taste and smell it within a few seconds following its introduction

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†Ether in oil is prepared by the Loeser Laboratory, Incorporated, New York City.

into the body. On the other hand, the oil does materially prolong its volatilization and absorption, because patients are able to taste and smell it for twelve to twenty-four hours. From this it appears that absorption of the ether begins immediately but, owing to the oil, is prolonged, and that excretion occurs principally by the lungs.

It is probably because of the slow absorption of such a small dose that a slight depressing effect is maintained on the central nervous system. This depressing effect acts as an anticonvulsant and sedative and appears to influence favorably the bronchospasm and the patient's apprehension.

Also, because of the slow excretion of the ether by the lungs, tenacious mucus apparently is loosened and dislodged from the mucous membrane of the bronchial tree. Expectoration thus is facilitated. It is the difficult expectoration of this mucus, whether present in small or large amounts, that produces much distress because, owing in part to its foreign-body action, patients cough violently in an attempt to remove it. By loosening the mucus, its expectoration is accomplished more easily and quickly and less energy (coughing) is expended to expel it.

Method of Administration

Ether in oil should always be injected intramuscularly, preferably in the gluteal or deltoid regions. Strict antiseptic precautions should be observed at all times. Immediately prior to the injection, the skin should be prepared antiseptically. For the injection, a 22-gauge intramuscular needle should be employed. Although a larger one permits a faster introduction of the material, this enhances the risk of rupturing a small blood vessel deep in the muscle tissue, which would allow seepage into the blood stream. Obviously, for this reason also, the injection should be made slowly, and after insertion of the needle the piston should be withdrawn slightly to ascertain the position of the needlepoint. If it is in a blood vessel the needle should be withdrawn and reinserted.

Effect of Injections

When ether in oil is injected intramuscularly, the effects on an asthmatic patient may be described as immediate and delayed. The immediate effects are fleeting, occur within a few seconds, quickly disappear and are relatively unimportant. The delayed action of the preparation is apparently extremely beneficial, is usually evident in about two hours and may last from several hours to a week or several months.

Immediate effects. Immediately following the intramuscular injection of ether in oil, the patient is able to taste and smell ether from his breath. This occurs within a few seconds to about three minutes and continues for twelve to twenty-four hours. Patients state that it is not unpleasant.

As soon as the needle is withdrawn, or even while administering the injection, most patients complain of slight to moderate, but not distressing, pain at the site of the injection. It has been described as a sharp, stabbing, burning or piercing type of pain, which disappears within a few minutes. No asthmatic patient thus treated has refused an intramuscular injection of ether in oil because of the slight pain it had produced in the past. At no time was there induration, edema, necrosis or abscess formation at the site of and as the result of the injection.

Following its administration, there is a slight increase in the pulse rate, usually about ten beats per minute. Its character remains unaltered. As a rule, the systolic blood pressure is slightly elevated (5 to 15 mm. of mercury). Occasionally the blood pressure may remain stationary or may even drop (about 10 mm.). The changes in both the pulse rate and blood pressure are transient, lasting about twenty minutes. These changes are undoubtedly due to the stimulating action of the ether. The patients, however, have not complained of palpitation and have experienced no ill effects.

About fifteen minutes after the injection, some patients occasionally have a slight feeling of dizziness and coldness of the extremities, particularly of the feet. The sensations disappear quickly, usually within a few minutes, and cause no alarm. These symptoms, more correctly described as side effects, are probably due to the odor of the ether that the patient obtains either while the injection is being prepared or, following the injection, from the taste. This mild side reaction is encountered in only a very few patients. In those in whom it occurs, it is no longer evident after the third or fourth injection.

Delayed effects. The therapeutic effects following the intramuscular injection of ether in oil become evident in about two hours. They are apparently due to the anticonvulsant and expectorant actions of the ether. Patients become quieter and breathe more easily. The ether also appears to have a favorable action on the bronchospasm. In cases in which epinephrine produces either partial or no relief, it again becomes effective if administered in one to three hours following the ether injection. Further, expectoration of tenacious mucus becomes easier. Whether the patient has "dry" asthma, with small amounts of a glistening, pearly material, or "moist" asthma, with large amounts of a thick, mucoid, yellowish-green substance, both types of which are difficult to expec-

torate, ether, excreted through the lungs, seems to hasten and facilitate the clearing of this substance from the bronchial tree. The elimination of this mechanical factor (tenacious mucus) immeasurably aids in terminating the attack.

Dosage and Results

Acute bronchial asthma. Of the three clinical groups considered here — acute bronchial asthma, chronic bronchial asthma and status asthmaticus — the first is the least important because, in an uncomplicated case, sooner or later the symptoms respond to the usual medications. However, there are patients who respond favorably but not completely and in whom palliative medication must be continued for several days until relief is obtained. In such cases, an intramuscular injection of ether in oil, repeated in four to six or twelve hours if necessary, appears not only to aid the symptoms but also to render epinephrine and ephedrine more efficacious. One or two injections are usually sufficient.

Six patients, having had an attack of acute asthma from two to five days, were thus treated. All of them responded fairly well but not satisfactorily to injections of epinephrine, 1:1000, and to a combination of ½ gr. of ephedrine sulfate, 2 gr. of aminophyllin and ¼ gr. of phenobarbital, given by mouth. Four of them received one intramuscular injection of ether in oil; the remaining 2 received two each. Within two hours, the asthmatic symptoms were rapidly controlled. The patients became quieter, were able to breathe more easily and expectorated more freely. Thereafter, the usual palliative medications effectively controlled the symptoms.

Chronic bronchial asthma. Patients in this group have usually had their asthma for years, some as long as thirty or forty years. They generally have asthma the year around and suffer many acute exacerbations. Some of them have developed emphysema, with or without a barrel-shaped chest, and in some a minimal amount of tubular or saccular bronchiectasis is present. These patients are constantly raising a thick, mucoid or yellowish-green substance. Its removal by coughing often produces much distress and aggravation of the symptoms.

In this group, ether in oil intramuscularly is extremely beneficial. Its administration renders expectoration much easier. The patients thus become more comfortable and, as the mucus and cough diminish, may even become symptom-free unless there are marked secondary changes (emphysema and bronchiectasis) or a fresh episode is encountered. The beneficial results may last for several months or longer.

The dose is usually one or sometimes two injections per week, and may be continued in conjunction with other approved treatment until the cough, wheezes and sputum are reduced to a minimum. It cannot be emphasized too strongly that intramuscular ether in oil is an adjuvant and that it is not intended to replace other therapeutic agents.

Three cases of chronic bronchial asthma were so treated. Expectoration increased considerably and, after four or five injections, the symptoms were markedly improved. In these cases, the administration of ether in oil was continued weekly for about three months.

Status asthmaticus. This disease presents a most distressing clinical picture. The patients are in a state of constantly acute asthma and do not respond appreciably to medication. They are referred to as adrenalin-fast cases. In these cases intramuscular ether in oil appears to be an excellent adjuvant. In about two or three hours following its administration, beneficial results may be noted. The patients become quieter, expectorate more freely and profusely, and other palliative medications become more effective. The dose, one ampule, should be repeated every four to six hours as indicated by the response and progress of the patient.

Two patients with status asthmaticus were treated. One received nine intramuscular injections of ether in oil, the other eleven. Although both these patients had chronic asthma and had never been completely free of their symptoms, one has remained symptom-free for more than four months, and the other for more than six months.

Summary

Ether in oil intramuscularly as an adjuvant for the treatment of bronchial asthma is suggested.

It appears to act as an anticonvulsant and expectorant, thus beneficially influencing the asthmatic state.

The good results obtained may last from several hours to several weeks or months and justify further clinical studies.

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CLINICAL NOTE

SUCCESSFUL POST-MORTEM CESAREAN SECTION

Report of a Case

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BECAUSE of the relative rarity of cases of successful post-mortem cesarean section, in the medical literature,[1-3] it is thought worth while to report the following case:

Case Report

H. M., a 24-year-old gravida III para I, entered the Cambridge City Hospital on January 19, 1941, with a chief complaint of cough and difficult respirations. Three days previously she had noted onset of cough, sore throat, generalized muscle aches and low-back pain, together with dyspnea. These symptoms all regressed except the cough and dyspnea, which had grown steadily worse. The cough was productive of thick yellow sputum. The patient had had no chill, chest pain or hemoptysis. She was seen by her family physician, who advised hospitalization.

The patient had had bronchial asthma for the preceding 8 years without treatment. She had one living child, 3 years of age. Her second pregnancy had resulted in a stillbirth. Her last menstrual period occurred about June 20, 1940, so that on entry she was slightly less than 7 months in gestation. The prenatal care had been adequate. She was first seen on October 30, 1940, with a blood pressure of 90/60; it was noted that she was nervous and apprehensive. On December 11 the blood pressure had risen to 136/70. She had gained 9 pounds, her weight at that time being 228 pounds. She was seen on January 8, 1941, and had no toxic signs or symptoms; the blood pressure was 152/76, and the body weight 232 pounds. She was not seen again until the day of admission.

Physical examination revealed a well-developed, obese white woman lying propped up in bed, wheezing and coughing. The temperature was 100.4°F., the pulse 134, and the respirations 36. Both lung fields were diffusely filled with fine moist expiratory rales. Occasional coarse inspiratory rales were heard over the bases posteriorly. Expiration was prolonged. The abdomen was obese, and there was a midline tumor mass extending two thirds of the way to the ensiform cartilage. The fetal heart was audible in the right paraumbilical region and was regular. The diagnoses at that time were seven-month pregnancy, bronchial asthma and grippe.

The patient was immediately given adrenalin, intravenous aminophyllin, calcium gluconate and 50 cc. of 50 per cent glucose intravenously, but respiratory distress continued. She was put into an oxygen tent. A portable chest plate was taken, the report being: "Mottled areas of increased density scattered throughout both lung fields. The appearance is consistent with an extensive bilateral bronchopneumonia." Sputum typing and blood culture were immediately done, and both were reported positive for Type 3 pneumococcus. Type 3 rabbit serum was obtained from the Massachusetts Department of Public Health, and the patient was skin-tested. The reaction was markedly positive to a 1:1000 dilution, and an ophthalmic test was positive to a 1:100 dilution. Advice was sought from Dr. Maxwell Finland of the Pneumonia Service of the Boston City Hospital. He emphatically advised that serum should not be given, and it was therefore withheld. Sulfathiazole was given in full therapeutic dosage.

On the morning of the 4th hospital day the patient was seen by the Obstetrical Service. They advised disregarding the pregnancy and treating the pneumonia, but added that in the event of death a post-mortem section should be considered. On the same day the patient rapidly became worse. The temperature rose to 105°F., and the pulse was over 160. The color remained good,—in the oxygen tent,—but the patient became comatose at about 11 p.m. Coarse moist rales were audible throughout both sides of the chest, and the fetal heart could not be heard in the presence of the loud gurgling respirations.

In spite of constant and energetic measures to restore the patient, she failed to rally, and preparations were hastily made for a post-mortem cesarean section. Terminally the respirations became short gasps with long intervals of apnea. The oxygen tent was kept going continuously, and the patient's color remained good. She was pronounced dead at 3:24 a.m., no fetal heart sounds having been heard for about 4½ hours. About 20 seconds later the abdomen was opened by a single midline incision, and the uterus sagged forward. The fundus was opened, and the baby was delivered manually. A small incision was inflicted on the baby's right cheek by accident when the uterus was opened. Alpha-lobeline was injected into the umbilical cord, which was apparently pulseless, and within a few seconds respirations were established. The infant, a female, was transferred to an incubator, and given oxygen as needed. Vitamin K was given and gavage feeding was begun within 24 hours. The early feeding consisted of water, glucose and whisky, later supplemented by breast milk.

At birth the infant weighed 3 pounds, 6 ounces. After an initial loss of 2 ounces in weight she made uneventful progress. She left the hospital after 7 weeks, weighing 6 pounds, and is at present in good health.

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MEDICAL PROGRESS

THE SULFONAMIDES*

I. Their Mode of Action and Pharmacology

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IT IS six years since Prontosil, synthesized by Mietzsch and Klarer[1] and proved to be effective against the hemolytic streptococcus in mice by Domagk,[2] first came to the attention of the English-speaking medical world as a potent chemotherapeutic agent in man, with Colebrook and Kenny's[3] report on its use in puerperal sepsis. There have been few more important medical discoveries, and it can be truthfully stated that the introduction of the sulfonamide drugs marked the beginning of a new era in medicine. Bacterial infections, most of which had been treated by purely symptomatic measures, suddenly became amenable to therapy, and the reduction in the mortality of such severe infections as hemolytic streptococcus meningitis, pneumococcal pneumonia and meningococcal meningitis has been little short of miraculous.

It is small wonder that there has been a flood of papers on the use of the sulfonamides or that those in practice have been somewhat confused by the rapidity with which the popularity of one new sulfonamide derivative after another has waxed and waned. The only justification for adding this report to the multitudes already written is that I have been struck by the need for a very concise and practical presentation of the present state of our knowledge of these drugs.‡ In this and the following article, an attempt will be made to summarize what has been learned in six years about their usefulness and limitations and to put this information in such a form that it will be helpful to those who are called on to use the sulfonamides in everyday practice. This type of presentation must necessarily be somewhat dogmatic. Since the sulfonamides play such an important role in both civilian and military medicine, the times will justify the repetition in condensed form of what can be found in the writings of many workers in the field of chemotherapy.

Reprints of articles in this series are not available for distribution, but the articles will be published in book form. The current volume is *Medical Progress: Annual, Vol. III, 1942* (Springfield, Illinois: Charles C Thomas Company, 1942. $5.00).

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‡There is one excellent manual, which every practicing physician would do well to own, *Guides to Therapy for Medical Officers*, War Department Technical Manual 8-210, obtainable from the United States Government Printing Office, Washington, D. C., for 25 cents. Section V (pages 110–135) covers sulfonamaide therapy briefly and accurately.

MODE OF ACTION

The intelligent use of these drugs presupposes an understanding of their mode of action. *There is overwhelming evidence that they act on the organisms to delay or completely to inhibit their multiplication and do not increase the defensive powers of the host.*

Resistance to pyogenic infections depends on the speed and intensity of the inflammatory reaction, which localizes the infection nonspecifically, and on the presence of specific antibody, which makes possible the destruction of organisms by phagocytosis or lysis. There is no evidence that the sulfonamide drugs act through either of these mechanisms. Nonspecific inflammatory localization is promoted by the time-honored measures of heat and rest, the former to increase circulation to the inflamed area, the latter to keep the drainage of lymph at a minimum and to allow minute thrombi to form about the focus in lymphatics and capillaries. Specific antibody may be administered when it is lacking, as in the serum treatment of pneumonia.

The virulence of pathogenic organisms, however, depends not only on their ability to secrete substances that inhibit inflammatory localization, such as streptococcal fibrinolysin, and their ability to escape destruction by the phagocytes in the early stages of infection, but also and above all on their ability to multiply in the tissues of the host. This property is fundamental to all pathogens, and the most invasive bacteria, such as those of anthrax and plague, are able to utilize the substances in the body fluids of the host so effectively that they multiply at an astonishing rate and overwhelm their victim. The sulfonamides attack this aspect of virulence. If a sufficient concentration of a sulfonamide drug is added to a tube of culture medium, the growth of susceptible organisms is inhibited. If sufficient concentration of a sulfonamide is present in the body fluids of the patient, these fluids become poor mediums for the growth of many species of micro-organisms, and thus infections with these organisms may be brought under control, by what amounts to a process of starvation of the

bacteria. However, the organisms are often only starved into submission, and their release from the inhibitory activity of the sulfonamide before the body's defenses have been able to localize them or destroy them, or before the bacteria have autolyzed, is followed by rapid multiplication and the return of signs of infection.

The most important observation on the mode of action of these drugs was the finding by a number of workers[4–7] that there are substances capable of inhibiting the bacteriostatic action of the sulfonamides. The only inhibitor substances that have been identified chemically are para-aminobenzoic acid and its esters, among which is procaine. These substances have been found in killed and autolyzed bacteria,[5–7] yeast,[8] autolyzed liver, pus and other tissue-breakdown products.[9, 10] MacLeod's demonstration of the presence of sulfonamide inhibitor in pus and of its absence from serum explains the marked difference in therapeutic response between rapidly spreading infections such as pneumonia and localized purulent foci such as empyema.[11] It is a point of great theoretical interest that just as only the para-form of aminobenzenesulfonamide is effective against bacteria, whereas the meta-isomers and ortho-isomers are relatively inert, so the para-form of aminobenzoic acid alone of its isomers possesses the ability to inhibit sulfonamide action.[8]

In vitro study of the effect of sulfonamides on bacterial growth has shown that the curves have the character depicted in Figure 1. At first, in the period A-B, growth takes place at the normal rate. This is known as the "*lag*" phase. At B some change occurs, and from B to C is the period of *bacteriostasis*. Under proper conditions the population may fall in the period C-D, and the bacteriostatic effect can be said to have been sufficient to become *bactericidal* (Curve 1). Under other conditions the events depicted by Curve 2 may occur, and there is a phase of "*escape*."

Two mechanisms may make this escape possible. Enough organisms may autolyze to liberate sufficient inhibitor substance into the medium to overcome the sulfonamide effect, or drug-resistant organisms may develop, capable of growing in the presence of the drug. Such drug-fast strains can be produced by passing organisms through mediums containing increasing concentrations of the drug.[12–14] That drug-fastness depends on the ability to synthesize more para-aminobenzoic acid is suggested by the observation that drug resistance does not develop in the presence of small amounts of the acid[13, 15] and by the studies of Mirick,[16] which showed that a drug-resistant pneumococcus synthesizes ten times as much para-aminobenzoic acid as its parent strain. In actual clinical practice, the development of sulfonamide resistance has been

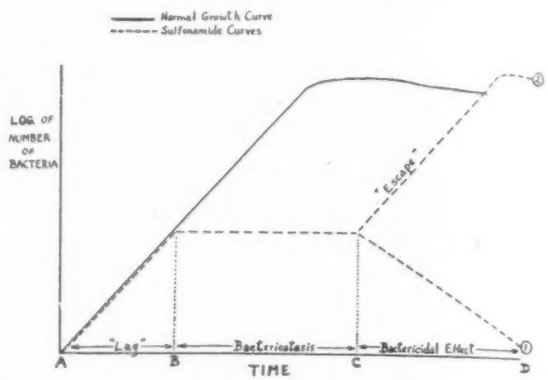


FIGURE 1. *Schematic Representation of Normal Growth Curve of a Micro-Organism and Its Growth Curve in the Same Medium Containing an Effective Concentration of a Sulfonamide Drug.*

observed only a few times,[15, 17, 18] but the fact that it may develop is an argument for treating infections intensively at the beginning.

The lag phase corresponds to the clinical observation that there is a period of several hours after chemotherapy is begun before a therapeutic effect is noticeable. This suggests that some change must occur either in the bacteria or medium during this period. There is proof that this change involves the organisms and not the medium, and that it is readily reversible.[19, 20] Recently Rose and Fox[21] have suggested that it is due to the exhaustion of a substance present in the parent bacteria, which cannot be synthesized by the bacteria in the presence of sulfonamide. Their evidence for this is that, at the minimal effective sulfonamide concentration, the bacteria divide only a fixed number of times before inhibition of growth occurs, no matter what the size of the inoculum or the character of the medium, provided it does not contain para-aminobenzoic acid.

In 1940, Fildes[22] propounded his theory that the sulfonamides and other antibacterial substances act by interfering with the metabolism of an essential metabolite ("an organic substance without which metabolism cannot proceed to the extent required by growth"). Since that time a series of papers from his laboratory have built up a convincing array of evidence for this hypothesis, and have placed the further development of sulfonamide therapy on a rational rather than an empirical basis.

Woods[8] identified para-aminobenzoic acid as the specific inhibitor of the action of the known sul-

fonamides. From his work, he suggested that sulfanilamide, by virtue of its chemical similarity to para-aminobenzoic acid, replaces the latter as the substrate for an enzyme concerned with the further utilization of this essential metabolite. Whether or not bacteriostasis or growth occurred in such a system, depends on the relative proportion of the two competing substrates. If the proportion of para-aminobenzoic acid to sulfanilamide was more than 1:5000, growth occurred; if less, growth did not, regardless of the absolute concentrations of either substance. Such a theory of competitive inhibition still does not explain why the critical ratio of para-aminobenzoic acid to sulfanilamide is 1:5000 with a given strain of micro-organism whereas the ratio of para-aminobenzoic acid to sulfathiazole with the same strain is 1:8, but it explains all other known facts very well. A partial explanation, at least, for the differences in bacteriostatic efficiency of the various sulfonamide drugs has been offered by Fox and Rose.[23] They found that the critical ratio of para-aminobenzoic acid to sulfonamide was much more nearly the same for the different drugs if only the concentration of ionized sulfonamide was considered. Schmelkes and his co-workers[24] have come to the conclusion that the active sulfonamide exists as an anion, and recently Cowles[25] has reported evidence further strengthening the hypothesis that ionization plays a decisive role in sulfonamide action.

One necessary assumption is that para-aminobenzoic acid is an essential metabolite for bacteria. Evidence for this has been provided by Park and Wood,[26] who showed that, in the presence of biotin, extremely minute amounts of para-aminobenzoic acid produced a marked stimulation of growth of *Clostridium acetobutyricum*. A practical application of the identification of para-aminobenzoic acid as a specific inhibitor of the bacteriostatic action of the sulfonamides is its inclusion in culture mediums so that organisms present in the blood and other body fluids of patients under sulfonamide therapy will grow at a normal rate.[27]

On the basis of Fildes's general theory and Woods's elaboration of it for the sulfonamides, it should be possible, from a knowledge of bacterial metabolism, to prepare chemotherapeutic agents which will inhibit the utilization of other essential metabolites. The validity of the hypothesis has been tested and supported in experiments conducted by Fildes's associates. By replacing a carboxyl group on an essential metabolite with a sulfonic group, the utilization of the metabolite may be competitively blocked by a sufficient concentration of the new and unnatural, but chemically similar compound. A list of those compounds already tried follows:

AUTHOR	ESSENTIAL METABOLITE	GROWTH-INHIBITOR
Woods[8]	Para-aminobenzoic acid	Sulfonamides
McIlwain[28]	Nicotinic acid	Pyridine-3-sulfonic acid
McIlwain[28]	Nicotinamide	Pyridine-3-sulfonamide
McIlwain[29]	Alpha-amino-RCOOH	Alpha-amino-RSO_3H
McIlwain[30]	Pantothenic acid	Pantoyl taurine
Fildes[31]	Indole; tryptophan	Indolacrylic acid

McIlwain[30] has proposed what he has called the antibacterial index for characterizing such systems. This is the ratio of the minimal effective concentration of the bacteriostatic agent to the concentration of the corresponding metabolite. Such a ratio is constant for any particular organism, although the absolute amounts of the two substances may vary over a wide range. The determination of such ratios, of course, involves the use of synthetic culture mediums of known composition, so that the concentrations of the substances being tested can be accurately measured. From a knowledge of such a ratio, of the concentration of the essential metabolite in tissue fluids and of the toxicity and absorption of the bacteriostatic substance, it should be possible to determine whether or not a new chemotherapeutic agent of this type can be expected to work in vivo against a particular organism.

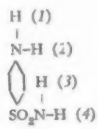
Thus, in seven years, chemotherapy has progressed from the more or less empirical discovery of an azo-dye, Prontosil, to the synthesis of new chemotherapeutic agents which can be designed to attack the most vulnerable facet of an organism's metabolism. It should not be forgotten that none of this progress would have been possible had not the laborious work of elaborating the growth requirements of bacteria been going on for many years. It is largely due to the work of men like Fildes in England and Mueller in this country that the science of bacteriology has been carried forward to the point where it can provide the tools for the further development not only of the field of chemotherapy, but of human nutrition as well.

Pharmacology of Sulfonamide Drugs

Besides an understanding of the way in which the sulfonamides act on bacterial infections, it is essential for a physician who uses these drugs to have accurate knowledge of their pharmacology. When drugs such as aspirin are used for the relief of symptoms, little more knowledge than the average layman possesses is necessary, but when poten-

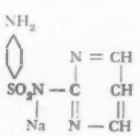
tially dangerous remedies are used in large doses for the treatment of serious diseases, detailed pharmacologic knowledge is as vital to the physician as are a knowledge of anatomy and a skilled technic to the surgeon performing a difficult operation.

The pharmacology of these drugs can best be presented in tabular form after a few general remarks. All the sulfonamides in common use are derivatives of sulfanilamide, which has this formula:



The numbers after the hydrogen atoms are to identify them for convenience in the text.

Two types of sulfanilamide derivative have come into clinical use. The first type involves a replacement of hydrogen atom (*4*) by some nucleus, from which the compound derives its name. Thus, sulfapyridine consists of sulfanilamide with hydrogen (*4*) replaced by the pyridine ring. These compounds are all more potent than sulfanilamide. However, they are much less soluble, and for that reason they are unsuited for parenteral use. The substitution of a sodium atom for hydrogen atom (*3*) renders them soluble in high concentrations and they may be injected intravenously as 5 per cent solutions in distilled water or saline solution. Thus the formula for sodium sulfadiazine is:



These sodium salts are quite alkaline and are extremely irritating if injected into the tissues outside of the vein. However, at 0.5 per cent strength they may be used subcutaneously in infusions.* *They must never be used intrathecally, as their alkalinity will produce irreparable damage to the nervous tissue.*

A second type of sulfanilamide derivative has been introduced by Marshall and his associates[32] as a result of their studies of sulfaguanidine, which was synthesized by Roblin and his co-workers. Sulfaguanidine is water-soluble to a considerable degree, but is absorbed very poorly from the bowel, so that high concentrations of the drug in the intestinal tract may be achieved while the blood level remains low. While sulfaguanidine involves a substitution of a guanidine radical for hydrogen atom (*4*), succinyl sulfathiazole, which is now being tested for its effect in the bowel, has a succinic acid chain coupled to the para-amino group replacing hydrogen (*2*). In the bowel the succinic acid is split off, liberating sulfathiazole, which is more potent than sulfaguanidine and is comparatively little absorbed in the large intestine.[33]

The present knowledge of the distribution of these drugs is the result of the development of accurate methods for their estimation by Fuller[34] in England and by Marshall and his co-workers[35] in this country. The method depends on the fact that sulfanilamide or its derivatives when coupled to N-(1-naphthyl)-diethyleneamine develops a purple-red color. This reaction is specific for the para-amino group and is accurate except in the presence of procaine, which is an ester of para-aminobenzoic acid. If, for example, novocain is allowed to enter the pleural cavity in preparation for thoracentesis, the fluid removed may appear to contain much larger amounts of sulfonamide than it actually does.

The important facts that should be known about each sulfonamide are its rate of absorption

TABLE 1. *Characteristics of the Sulfonamide Drugs.**

Drug	Rate of Absorption	Degree of Conjugation	Rate of Excretion		Desired Blood Level	Incidence of Common Toxic Symptoms				
			Free	Conjugated		Subjective Discomfort	Nausea and Vomiting	Acute Hemolytic Anemia	Mild Anemia	Granulocytopenia
					mg./100 cc.					%
Sulfanilamide	Rapid	Usually about one third	Rapid	Fairly rapid (soluble)	8–15	Very frequent	Frequent	Fairly frequent (2–3%)	Almost constant	<1
Sulfapyridine	Irregular	Usually high	Moderately rapid	Slow (moderately insoluble)	5–10	Frequent	Very frequent	Rare	Frequent	<1
Sulfathiazole	Rapid	Usually less than one third	Very rapid	Rapid (very insoluble)	3–7	Rare	Frequent	Very rare	Rare	<2
Sulfadiazine	Fairly slow	Usually less than one third	Slow	Moderately slow (soluble)	8–15	Very rare	Rare	Rare	Moderately rare	<1

*Percentages where used are from Long's[28] published statistics.

*There is recent evidence that concentrations as high as 2 per cent are tolerated on subcutaneous injection.

and rate of elimination, since on the balance between these depends the level achieved. Absorption of the substituted sulfonamide takes place mainly in the stomach. It is modified by food, and is most rapid before meals but most complete after meals.[36] Alkali may play a role in increasing the amount absorbed. Elimination may occur in two ways, either by excretion of the unchanged or free drug in the urine or by conjugation of the free drug to a combined form, probably in the liver. The conjugated form, which has little therapeutic activity, is excreted in the urine also.

FREE SULFANILAMIDE — CONJUGATED OR ACETYL SULFANILAMIDE

The determination of the amount of conjugated sulfonamide present is made by determining the free drug in the usual manner, then hydrolyzing the sample with heat and acid for one hour, which converts the conjugated to the free form, and redetermining the amount of drug.

The distribution of these drugs within the body varies considerably. This may depend in part on differences in ionization already mentioned, but even more on the binding of the different drugs by the proteins of the plasma, as demonstrated by Davis.[37] At one extreme, sulfanilamide appears to traverse membranes with little difficulty and is found in the red cells and in the spinal fluid in concentrations similar to those in plasma, whereas at the other extreme, sulfathiazole remains chiefly in the plasma, appearing in both red cells and spinal fluid in considerably lower concentrations. In most inflammatory exudates, these drugs are found in concentrations closely approximating those of the blood.

Toxic effects follow a general pattern for the whole group, with some differences between individual drugs.

Nervous symptoms are always present to greater or less degree, and usually appear soon after therapy is begun. These vary from mild lassitude or anorexia through nausea and vomiting to frank psychosis. Nausea and vomiting are listed as nervous, since they are clearly central in origin. The mechanism of these symptoms is not yet clearly understood, although it has been suggested that they represent subjective reflections of disturbances in metabolism of nervous tissue produced by the drug. In any case, acute poisoning of animals with large doses of the sulfonamides results in convulsions and spasticity, evidences that the central nervous system has suffered most severely. Various vitamin preparations, particularly nicotinic acid, and oxygen have been recommended for their control, with different results in the hands of different investigators. The advent of sulfadiazine, which produces very little subjective disturbance, has made such accessory therapy unnecessary. An important practical point is that an ambulatory patient taking sulfonamides should be warned that his reaction time may be slowed. Special care should be observed in driving a car, crossing streets and performing manual work.

*Acidosis** occurs only when sulfanilamide is used, since it is associated with inactivation of the enzyme, carbonic anhydrase. This inactivation has been shown to be due to the sulfonamide group and not to the para-amino group on which antibacterial activity depends.[39, 40] In the substituted sulfonamides the sulfonamide group is covered by the substituent nucleus, and thus cannot react with the enzyme. Bicarbonate of soda diminishes acidosis with sulfanilamide, but is not necessary with the other drugs.

Cyanosis, so prominent and unsightly a manifestation of sulfanilamide therapy, is slight with the other drugs. It has been proved to be due to a combination of methemoglobin[41] and the colored oxidation products of sulfanilamide, some of which are responsible for the oxidation of hemoglobin methemoglobin.[42] It can be reversed by the reducing action of methylene blue,[43] but usually does no harm. However, the production of methemoglobin by

*This acidosis is characterized by a loss of sodium ions in the urine and a reduction of the bicarbonate and sodium ions and an increase of the chloride ions in the plasma. With this clinical picture, hyperventilation develops. These changes are reversed when the drug is stopped.[38] Bicarbonate of soda acts only as a symptomatic remedy that relieves the hyperventilation to some extent.

TABLE 1 (*continued*).

INCIDENCE OF HYPERSENSITIVITY RASH	FEVER	TENDENCY TO SENSITIZE	INCIDENCE OF RENAL COMPLICATIONS	COMMENT
%				
2	Frequent (10%)	Moderate	Very rare	Seldom used because of subjective discomfort, low potency and anemia
2	Fairly frequent (4%)	Slight	Hematuria, frequent; oliguria, occasional.	Potent, but seldom used because of vomiting and irregular absorption
5	Very frequent (10% or more)	Marked	Hematuria, occasional; oliguria, frequent.	Very potent and well tolerated, but most apt to cause renal complications and to sensitize, causing rash and fever on subsequent administration. Difficult to maintain desired blood level because of rapid excretion.
2	Moderately rare (2%)	Slight	Hematuria, occasional; oliguria, rare.	Not quite so potent, but best tolerated and high blood levels easily achieved because of slow excretion. Treacherous, since serious toxic reactions may occur after cessation of therapy, also owing to slow excretion.

sulfonamide therapy is of possible importance in aviation medicine. Methemoglobin will not carry oxygen, and aviators undergoing chemotherapy should suffer from anoxia at lower altitudes than normal men. Since anoxia is one of the chief limiting factors in aerial combat, these men should be grounded until they are well.

Blood disturbances are all too common and may assume almost any form. Acute hemolytic anemia, which may be severe enough to cause hemoglobinuria, is rare except with sulfanilamide. It generally comes on in the first few days of therapy. This type of anemia can be produced by many chemically related substances, notably para-aminophenol,[44] which may possibly be produced in vivo from sulfanilamide. Low-grade anemia, which may be remedied by transfusion, is a common accompaniment of prolonged sulfonamide therapy. The granulocytes are particularly sensitive to many compounds derived from benzene, and therefore agranulocytosis and granulocytopenia may occur with all these drugs. Thrombocytopenia, with purpura, likewise has been described with all the drugs in common use, although it is extremely rare.

Skin manifestations are manifold. Various types of erythematous eruptions — particularly morbilliform or nodose — have been observed. A few cases of exfoliative dermatitis have followed sulfonamide therapy. These rashes frequently accompany fever, lymphadenopathy, splenomegaly and arthralgia, to form a picture quite comparable to serum sickness. Furthermore, these toxic reactions occur most frequently from the fifth to the fifteenth day after the beginning of therapy, and if a patient once has such a reaction, the readministration of a small dose of the drug will suffice to precipitate the reaction in the space of a few hours. This phenomenon is analogous to that of accelerated serum sickness.

Fever is one of the commonest and most confusing toxic reactions, especially when it occurs without rash, arthralgia or lymphadenopathy. Its mechanism is not understood any better than that of other drug sensitivities, such as the ninth-day erythema of arsphenamine treatment, to which it is entirely comparable. As yet nobody has been able to demonstrate the presence of specific antibodies in patients who develop this form of hypersensitivity. An attempt to transfer hypersensitivity passively to normal people with the serum of the most sensitive patient observed was entirely unsuccessful.[45]

Visceral damage may occur in sulfonamide therapy. Hepatitis with jaundice has been reported, but it is very rare. Renal damage simulating the nephrosis of bichloride poisoning may occur with rather small doses of sulfathiazole and probably represents a true toxic nephritis.[46] Myocardial lesions occur pathologically in patients receiving sulfathiazole, and intraventricular block has been observed in a patient with severe intoxication.[45, 47] One or two cases of encephalopathy from sulfathiazole have been reported, and are possibly analogous to the hemorrhagic type of encephalitis, which is a rare but very severe form of intoxication with the organic arsenicals.

Oliguria due to precipitation of the drug has been observed only with the relatively insoluble substituted sulfonamides and not with sulfanilamide, which has a relatively high degree of solubility. As the glomerular filtrate passes down the renal tubules, it is concentrated by the resorption of water. This may result in a concentration of the urine to a point where the solubility of the sulfonamide or its acetylated form is exceeded and precipitation occurs.* Hematuria, calculus formation or tubular obstruction may result, with consequent oliguria and eventual renal shutdown unless something is done quickly to prevent it.

That sulfonamide therapy produces not only functional and chemical disturbances in the patient, but morphological changes as well, has recently been conclusively proved. A number of authors[46–48] have described multiple small nodules of miliary necrosis in the tissues of patients receiving sulfathiazole. Rich,[49] in an investigation of the pathology of serum sickness, has described lesions indistinguishable from those of periarteritis nodosa. It is significant that most of his patients had received sulfonamides as well as serum and that he found similar lesions not only in a case of serum sickness before the days of chemotherapy, but also in a patient who had received nothing but sulfathiazole. If this finding can be substantiated, it will provide pathological evidence for the essential similarity between the hypersensitivity developing as a result of sulfonamide administration and that following foreign serum.

The pharmacologic properties of the individual sulfonamide drugs are assembled in Table 1 in such a way that they are readily available for the physician who must choose which drug he will use. When the individual drugs are compared, certain differences between them do stand out clearly. Sulfanilamide is conspicuous for the frequency of cyanosis, acidosis and acute hemolytic anemia. Sulfapyridine is characterized by two outstanding properties — its tendency to produce nausea and vomiting and its antipyretic action.[50, 51] Of all the drugs in this group it is the only one which is antipyretic, and thus temperature is not a reliable criterion for control of infection with sulfapyridine. Sulfathiazole and sulfadiazine are both remarkably well tolerated by most patients. However, there is increasing evidence that sulfathiazole is a fairly toxic drug, and unfortunately, sulfadiazine, although it produces severe reactions less frequently, is treacherous because of its slow excretion.

*Bicarbonate of soda has been recommended to make the urine more alkaline and thus prevent crystal deposition. It is doubtful whether the urine can be rendered sufficiently alkaline to alter markedly the solubility of these compounds. Soda may be given when hematuria or oliguria occurs, but its routine administration is not justified, because these patients already have to take so many pills.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

CASE 28521

PRESENTATION OF CASE

First admission. A twenty-three-year-old single English typist was admitted because of chronic productive cough of thirteen years' duration.

Nineteen years prior to admission the patient suffered with a severe attack of whooping cough. The cough persisted for a year and finally cleared up spontaneously at a seashore resort. During the succeeding seven years she had recurrent colds, sore throats and several episodes of "draining ears." Her "tonsils and adenoids were snipped" several times, and following the last tonsillectomy twelve years ago, she developed a chronic cough. During the next ten years the cough gradually became severer and more productive so that at the time of admission she raised half to three quarters of a glassful of foul-smelling greenish sputum each day. The greatest amount was raised in the morning and in the evening on return from work. The patient had recently noticed blood streaking of the sputum, and at times she expectorated large tenacious plugs. She attempted postural drainage, but this proved too strenuous for her.

Four years before entry many nasal polyps were removed. Two years previously a radical antrum drainage was established without improvement. At that time, she suddenly developed severe sharp pain in the left chest. Her physician believed that she had pleurisy and accordingly immobilized the chest with adhesive strapping, but this provided little relief. Two weeks later, x-ray examination apparently demonstrated a collapsed left lower lobe. A lipiodol study revealed bronchiectasis of the left lower lobe. Three weeks before entry, following an episode of coughing, she raised a quart of blood, but there had been no recurrence of the massive hemoptysis.

The family and past histories were noncontributory.

Physical examination disclosed a poorly nourished, asthenic girl in no acute distress. Examination of the heart was negative. A few coarse rales were audible over the entire left lung posteriorly.

The blood pressure was 130 systolic, 90 diastolic. The temperature was 98, the pulse 90, and the respirations 20.

Examination of the urine revealed a +++ test for albumin. A review of the chest x-ray films after lipiodol instillation, taken at another hospital, showed left-lower-lobe bronchiectasis. No disease was seen in the left upper lobe and right lung.

The patient was discharged unimproved on the third day after admission.

Second admission (four months later). A left lower lobectomy was performed. The patient had a stormy postoperative course. She developed atelectasis of the left upper lobe and encapsulated empyema at the apex. Bronchoscopy revealed a great amount of mucus in the left bronchus, but no mucous plug was seen obstructing the bronchus to the upper lobe. The empyema was tapped, and very small amounts of thick material were recovered. This fluid was negative on culture.

Eight weeks after lobectomy, the left third rib was resected, and open drainage established. Multiple pockets containing air and a thin clear fluid were found over the anterior and superior surfaces of the upper lobe. After this, the temperature and pulse, which had been elevated slightly each day, gradually returned to normal. The patient was discharged four months after admission.

Third admission (one month later). One week after discharge the lobectomy incision opened at the lower end and discharged a mucoid material. The patient had a slight fever, and her physician inserted a tube in the wound for drainage. The upper empyema-drainage tube discharged a moderate amount of pus. The patient was emaciated and appeared to be chronically ill. There were three tubes in the left chest wall, two in the third intercostal space and another in the sixth intercostal space. An x-ray film of the chest revealed the tip of the upper drainage tube lying anteriorly and the lower tube posteriorly in the chest. There was still density throughout the entire left lung field except for a small collection of air at the extreme apex. The heart shadow was still markedly displaced. The patient gradually improved on open chest irrigation and left the hospital a month later.

Fourth admission (two years later). Following discharge the patient soon developed empyema on the right side, which was drained by tube at home. She spent the greater part of the next three months in an oxygen tent at home. A slow recovery was made and she was not out of bed to any extent till the following summer — about a year later. The patient then moved to a farm, where improvement was marked. Her weight rose from 65 to

98 pounds, her appetite increased, she felt stronger, and her cough lessened. She continued, however, to produce about 100 cc. of foul sputum daily. She had had slight hemoptysis on only three occasions in the previous few months. Occasionally she had pains in her left upper chest, accompanied by a "congested feeling," anorexia and a "dragged-out sensation." Her symptoms were progressive to the time of admission.

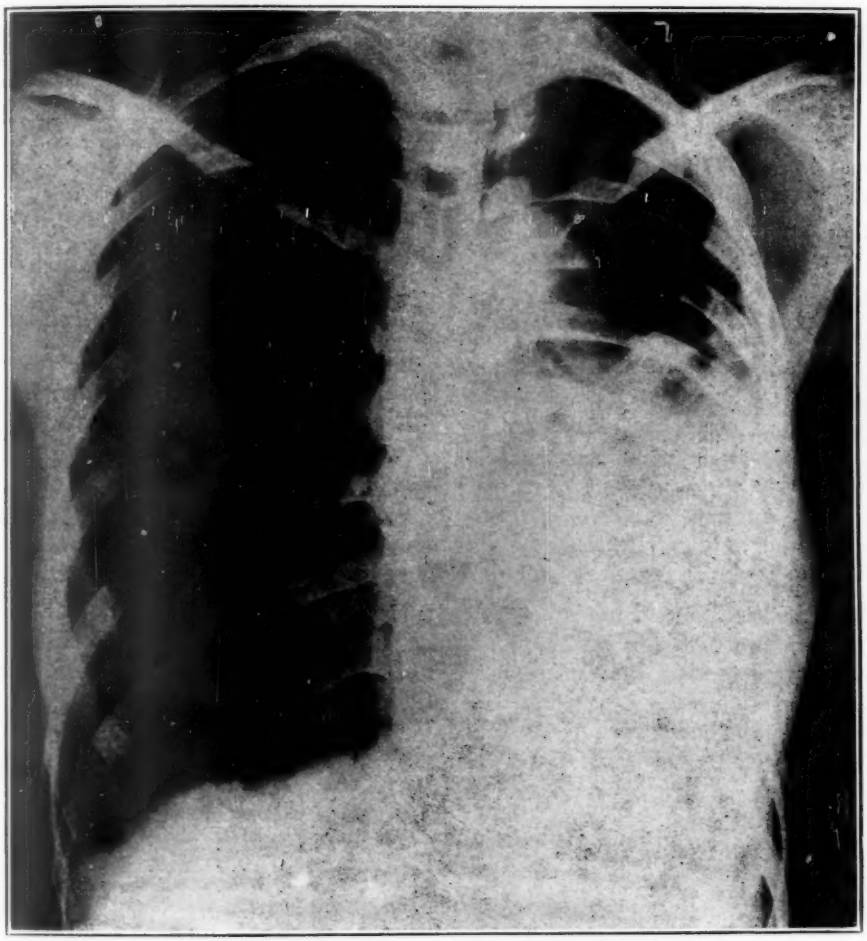

FIGURE 1. *Roentgenogram Taken at the Fourth Admission Showing the Apparent Pneumothorax in the Apical Portion of the Left Pleural Cavity.*

Physical examination showed dullness, increased tactile fremitus and decreased breath sounds over the left upper lobe. Over the left lower lobe there were dullness, flatness and absent breath sounds and tactile fremitus. There were a few rales at the right base. The fingers were clubbed.

X-ray films showed that the lower half of the left lung field was completely opaque and that there apparently was a pneumothorax occupying the apical portion of the left pleural cavity (Fig. 1). In the left midchest were several rounded areas of diminished density, without fluid levels, communicating with a dilated left main bronchus. The left lower main bronchus ended abruptly, apparently at the site of the lobectomy. The mediastinum was displaced to the left but showed no respiratory shift. The right-lower-lung field showed increased markings with some apparent honeycombing, which had the appearance of bronchiectasis. In the lateral view this was seen to occupy the region of the middle lobe.

An operation was performed on the seventh hospital day.

DIFFERENTIAL DIAGNOSIS

DR. JOHN W. STRIEDER:* This is a long case and demonstrates many of the vicissitudes through which a patient who has had some of the complications of major thoracic surgery goes. It is probably better to take it up in sections and to comment as we go along.

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What is the significance of the attack of whooping cough? I think that is difficult to say without entering into a long discussion of the etiology of what may be the final diagnosis. The cough persisting for a year and then clearing up suggests that the patient had pulmonary disease that antedated the attack of whooping cough.

The tonsillectomy, twelve years previously, brings up the question of its relation to the subsequent course. She had no acute episode following tonsillectomy as she would have had had she developed putrid or nonputrid lung abscess as a result of the aspiration of infected secretions. The fact that the cough gradually became more severe "during the next ten years," in other words that she survived that ten years of cough, seems to me to be against acute lung abscess as a complication at that time. She raised more sputum in the morning and evening, which is usual because patients with chronic pulmonary suppuration have an opportunity during those twelve-hour intervals of puddling secretions and subsequently raising large amounts. She coughed up tenacious plugs, which may well have been fibrinous casts. It is interesting that, in patients with bronchiectasis, chronic sinusitis is a common complication that goes hand in hand with it. As Dr. Churchill has suggested, bronchiectasis is simply another infected sinus.

The question whether the atelectasis arose as a complication of the antral operation comes up. I should like to know what the anesthesia was. However, we all realize that atelectasis can be a complication of any surgical procedure under any anesthesia, whether local or general.

Hemoptysis of a quart of blood, of course, is not unusual in various types of chronic pulmonary disease, particularly bronchiectasis. Hemoptysis as a complication of bronchiectasis is commoner than hemoptysis as a complication of pulmonary tuberculosis. Since I have never seen a fatal hemoptysis in a patient who has bled as a complication of bronchiectasis, it must be very rare. It usually suffices to stimulate the patient to seek treatment, however, and in that connection it often serves a purpose.

The +++ test for albumin with the chronic pulmonary situation suggests chronic amyloidosis.

May we see the bronchograms? I do not know what Dr. Robbins will think of them, but to me, with the exception of the lateral view made earlier at another hospital, they contribute very little.

DR. LAURENCE L. ROBBINS: I think there is definite evidence of bronchiectasis in the left lower lobe.

DR. STRIEDER: These oblique views do not show it. Do you think that is something down there, below the shadow of the diaphragm on the left?

DR. ROBBINS: No; that is possibly an artefact. If it is anything of significance it is very poor filling.

DR. STRIEDER: The anteroposterior view, without lipiodol, shows atelectasis and that is all.

DR. ROBBINS: Yes. In addition to a very slight shift of the mediastinum to the left there is a dense line of increased density, which is consistent with a collapsed lower lobe.

DR. WILLIAM B. BREED: Do you mean to say that that dense line is the left lower lobe in its entirety?

DR. ROBBINS: No; but it is the sign that shows the edge of the collapsed lobe. Here is the triangular area of density that extends to the hilus, and this line is the edge of the lobe.

DR. STRIEDER: Up to this point the story is that of bronchiectasis. One thing not mentioned is bronchoscopy. To rule out the possibility of underlying foreign body, of bronchial adenoma or of other tumor, even in so young a patient, I make it a routine, in my clinic, to perform bronchoscopy on all patients with bronchiectasis. After lobectomy was done, bronchoscopy was performed, but there is no mention made of any lesion except for abundant secretions in the left main-stem bronchus. Conceivably other lesions could be overlooked because we assume the bronchoscopy was done for aspiration, and under the circumstances it is understandable that a pre-existing lesion could possibly be missed. I think it is not necessary to have a so-called "mucous plug" in the bronchus to the left upper lobe to have atelectasis of that lobe. At that time the patient had had the left lower lobe removed, and secretions in the left main bronchus would occlude the left upper bronchus so that atelectasis could occur.

We must assume that the cultures of the so-called "empyema" persisted negative over the eight-week period during which she was observed, and that drainage was undertaken perhaps with reluctance. The operative findings were also unusual for empyema, that is, if it was empyema due to pyogenic or anaerobic organisms, which might well be a complication of lobectomy. It leads one to suspect that perhaps the pathologic process was intrapulmonary rather than intrapleural and that the drainage established was actually in the lobe.

The discharge of mucoid material suggests two things: first, that the patient had opened a bronchopleural fistula and that mucoid secretions were coming from the open bronchus and, second, that she had pulmonary cyst of some sort with a communication with the pleural cavity and in turn with the incision. The mucoid drainage then became purulent, which it might well do as the result

of drainage of some weeks' standing, but there is no mention that the pus was mucopurulent in character.

Probably there was no bronchopleural fistula. This patient could tolerate open drainage with irrigation, and it seems likely that she would have had severe cough and other unpleasant symptoms if there was an open bronchus communicating with the cavity. So we are reduced to saying that either she had empyema without bronchopleural fistula, or that she had an intrapulmonary cyst without patent bronchial communications. While this preoperative film is up, I should like to ask Dr. Robbins if he attributes any significance to the suggestive annular shadow in the left apex.

DR. ROBBINS: It could be a bleb, but I cannot be positive on this film alone. I do not think it is a cavity.

DR. STRIEDER: It certainly suggests cyst, and I believe there is a pathologic process in the apex.

DR. ROBBINS: In fact there could be several small blebs in a group.

DR. STRIEDER: This was the first-admission film, and I point out the suggestion of an annular shadow in view of what is to follow.

DR. ROBBINS: For comparison this is a film taken on the last admission (Fig. 1) and shows what appear to be cavities in which there is fluid, as well as this larger one, which may be a loculated air cavity within the pleural cavity. Drainage tubes enter the chest. This is the area of resection for the lobectomy.

DR. STRIEDER: The fact that there was a large area of decreased density in the apex, anteroposteriorly, in a patient with atelectasis of the left upper lobe following left-lower lobectomy is not significant other than that this configuration is apt to denote pleural space in x-ray films. Under these circumstances I think we are justified in saying no more than that this was an intrapleural lesion.

We are therefore again thrown back on two possibilities: a residual intrapulmonary lesion, in view of the foregoing films, and an empyema without bronchopleural fistula. Despite the fact that the patient did not cough on irrigation, which is consistent with the latter, it seems to me unlikely that that was the situation.

I think we have to say there is a possibility of pulmonary cyst in the left upper lobe.

DR. ROBBINS: In this film, there is an air-filled space in the apex and there are several areas of rarefaction in the area of density in the left midlung field. These represent air-filled cavities. This could be air in the pleural cavity, but I think we have seen at least one case in which there was a huge cavity in the apex that contained air, and one cannot very well tell the difference between them.

DR. STRIEDER: Can you offer any comment about this drainage tube entering into the intrapulmonary lesion?

DR. ROBBINS: Not from this film.

DR. STRIEDER: The anteroposterior view suggests to me that the lung is above the point of entrance of the drainage tube, and I think we have to take that into consideration, even though a lateral film is not available.

The problem resolves itself into a discussion of why, after left lower lobectomy for bronchiectasis, this patient continued to have symptoms of pulmonary suppuration and, as a corollary, what was the nature of these complications because of which she failed to improve. In such a complex situation the key to the solution, I think, lies largely in the x-ray films plus such other diagnostic procedures as we are able to apply, such as bronchoscopy. In this particular case, the result of bronchoscopy is not reported, but I think we can go along on supposition. If we can accept the report of the X-ray Department, based on films that are not here at the moment, there was bronchiectasis of the right middle lobe, which would account for the cough, and also intensive disease on the left side, and I think we are justified in assuming that the disability was due to the residuals in the remaining left upper lobe. The x-ray findings, the negative cultures of the material obtained on thoracentesis and the mucoid secretions strongly suggest cystic disease. Persistent atelectasis of the left upper lobe in a patient who has had left-lower-lobe lobectomy usually means obstruction of the bronchus by mucoid secretions or persistent underlying disease in the remaining lobe. That is, a patient whose remaining upper lobe stays collapsed after lower lobectomy, despite all measures to inflate it, usually has bronchiectasis or another related lesion in this lobe. On the information at hand I am unable definitely to rule out bronchial adenoma as a cause of the obstruction of the upper lobe, but I shall say that this patient probably had congenital cystic disease of the left upper lobe.

DR. TRACY B. MALLORY: Are there any questions or comments?

DR. BENJAMIN CASTLEMAN: Do you not think that, if she had congenital cystic disease of the upper lobe, the condition would have been at the first operation?

DR. STRIEDER: Not necessarily, for a variety of reasons. The upper lobe may have been completely held out by adhesions and the operator may not have thought it wise to explore farther,

knowing that the patient had disease in the left lower. Small cysts may not be palpable through surrounding normal lung tissue.

Clinical Diagnosis

Bronchiectasis of left upper lobe.

Dr. Strieder's Diagnosis

Congenital cystic disease, left upper lobe.

Anatomical Diagnosis

Cystic bronchiectasis of left upper lobe.

Pathological Discussion

Dr. Mallory: I am sorry Dr. Churchill is not here to discuss this case since he could give us much additional information. He was able to mobilize the upper lobe readily and inspect it freely at the time he removed the lower lobe. He did not see any evidence of cystic disease and felt quite satisfied with the examination.

The major interest in this case is the anatomic finding in the upper lobe, after resection. The apex of the lung was occupied by an enormous cystic cavity. Across it ran a threadlike bridge, probably a persistent artery. In the lower part of the lung there were numerous ordinary bronchiectatic cavities, and between these cavities there was a great deal of fibrous pneumonitis and virtually no aerated pulmonary parenchyma. On the basis of the facts that at the time of the first operation it was possible to visualize the upper lobe quite well and that no suggestion of cystic disease was seen, Dr. Churchill and I believe that this must have been an acquired cyst or bronchiectatic cavity, not a congenital one, and that the period of this patient's history between the first and fourth admissions represents the time required for the development of an extreme grade of bronchiectasis. One could, of course, argue that some bronchiectasis was present at the time of the first operation, but I think it is safe to say that no massive cyst of this character could have been present. The specimen as it now appears is one that I think all pathologists who believe in congenital cystic disease would accept as such, and yet our own interpretation is the opposite. We think this was acquired bronchiectasis rather than cystic disease.

Dr. Strieder: Would you be influenced by the fact that she did have persistent atelectasis, suggesting that she might have had previous bronchiectasis?

Dr. Mallory: It may be that the persistent atelectasis represents the cause of bronchiectasis. There is a great deal of debate on that point. I have always personally believed that persistent atelectasis is an important cause of bronchiectasis.

CASE 28522

Presentation of Case

A sixty-two-year-old white male bundle clerk entered the hospital with the complaints of swelling of the legs and abdomen, dyspnea and frequent vomiting of three weeks' duration.

The patient dated the onset of his present illness from an accident nine months before when he slipped on a sidewalk curbing and sprained his right knee and ankle, which laid him up for five weeks. Following this period he was able to resume work and was comfortable in the daytime but was awakened several times every night by cramps in his calf. Six months previously he had developed a "dry eczema" on the dorsum of the left foot over the second and third toes. He described the lesion as a red spot the size of a five-cent piece containing many still redder spots within it. It did not hurt or itch. A change of shoes, suggested by a chiropodist, did not help, and the "eczema" slowly spread in the course of six weeks over the entire malleolus and up the internal aspect of the left calf. At that time a similar rash appeared on the dorsum of the right foot; then it in turn spread up the right leg at a rapid rate. Spots soon appeared above both knees, then on the outer aspects of both thighs, and the individual lesions began to coalesce. The lesions itched considerably but were not painful. Whitewash relieved the itching but not the spread of the lesions. During the following two months, lesions appeared in a spotty distribution over the abdomen, chest, shoulders and the flexor surfaces of the elbows and wrists. The patient observed that although these lesions in the upper part of his body were "rash-like" the ones below the knees became fiery red and blood seemed to collect beneath the skin. Vitamin B complex and haliver oil were given without improvement.

He then consulted another physician, who reported that his entire trunk and extremities were covered with a blotching erythema and an underlying fine purpura. The lower legs were studded with large perifollicular purpuric spots. There was also slight edema of the shins, and the right lower leg was distinctly swollen. A diagnosis of toxic erythema with purpura was made, and vitamin K was prescribed. The patient took 160 tablets over a period of forty days with apparent improvement; the rash disappeared from the trunk, arms and upper legs but persisted in purpuric form below both knees.

One month before entry, although the skin lesions had not changed in extent or character, the patient returned to his physician's office complaining of lower abdominal discomfort, nausea

and occasional vomiting of seven days' duration and abdominal distention of four days' duration. For seven days his legs had been swollen. His bowels had moved daily with the aid of his habitual "three quarters of an ounce" of milk of magnesia.

Physical examination at that time showed probable ascites and an icteric tint to the scleras. The hemoglobin was 14.6 gm., the red-cell count 5,000,000, and the white-cell count 6500 to 8600, with 74 per cent polymorphonuclears, 21 per cent lymphocytes, 4 per cent monocytes and 1 per cent eosinophils. The blood smear was not remarkable; the platelets were slightly decreased. The icteric index was 25, and the nonprotein nitrogen 30 mg. per 100 cc. The total protein was 6.15 gm., the albumin 3.58 gm. and the globulin 2.57 gm. per 100 cc. The bleeding time was 2½ minutes, and the clotting time 7 minutes, with normal clot retraction. The prothrombin time was normal. The corrected sedimentation rate was 8 mm. per hour. The blood Hinton reaction was negative. The urine showed a specific gravity of 1.020, with a slight trace of albumin and a slightest possible trace of bile by the foam and iodine tests. The sediment showed rare white and red cells and innumerable hyaline and granular casts. A gastrointestinal series showed a normal stomach and duodenum; no esophageal varices were seen.

One week prior to entry it was found that the edema of his legs had progressed upward to the thighs. He complained of much unlocalized pain in both legs, especially on the left. An abdominal paracentesis was done, but the amount of fluid withdrawn and its character were not recorded. Digitalis and Salyrgan were prescribed.

The past history included severe poliomyelitis at the age of two and a half, with temporary paralysis of the entire right side of the body, followed by gradual return of motor function. The right extremities remained slightly weak, however, and scoliosis developed. The patient had an attack of jaundice at the age of twenty. The family history was noncontributory. He denied venereal disease and the use of alcohol. He had gained 13 pounds during the preceding year.

Physical examination showed an obviously ill and uncomfortable man with jaundice of the skin and scleras. Both lower legs were covered with purpuric spots, some of which appeared to be fresh; others were fading. There was pitting edema of both legs up to the knees, but the patient stated that this had decreased considerably during the previous week, during which he had received digitalis and Salyrgan. The spine showed marked scoliosis in the upper thoracic and lower cervical regions, and the chest considerable consequent deformity. The size of the heart could not be determined by percussion, and the apex impulse was neither seen nor felt. The examiner's impression, however, was that it was not enlarged. The sounds were of fair quality, and the aortic second sound was recorded as equal to the pulmonic. There were no murmurs. The rhythm was regular, at a rate 90 to 100. The neck veins were not distended. The lungs were clear. The abdomen was markedly distended, and there was shifting dullness in the flanks. Large veins could be seen in the anterior abdominal wall, but there was no hum audible at the umbilicus. A tender liver edge could be felt five fingerbreadths below the right costal margin and about the same distance below the ensiform in the midline; its upper border was percussed at the fourth interspace. The spleen could not be felt. Rectal examination showed external hemorrhoids and questionable enlargement of the left lobe of the prostate.

The blood pressure was 110 systolic, 85 diastolic. The temperature was 98.8°F., pulse 100, respirations 25.

Laboratory determinations showed a hemoglobin of 15.5 gm. and a red-cell count of 4,250,000. The white-cell count was 10,500, with 72 per cent polymorphonuclears, 18 per cent lymphocytes and 10 per cent monocytes; the smear was not remarkable. The hematocrit was 56 per cent. A single urine examination showed a specific gravity of 1.003 and gave a + test for albumin; there was no sugar or bile. The sediment showed 3 red cells and rare white and epithelial cells per high-power field. A stool was tan colored and contained bile; the guaiac test was negative. The serum nonprotein nitrogen was 82 mg. per 100 cc., and the prothrombin time 41 seconds (normal, 22 seconds). The liver function test showed 95 per cent retention of the dye in the serum. The serum protein was 7.8 gm., the albumin 4.5 gm., and the globulin 3.3 gm. per 100 cc. An electrocardiogram was interpreted as follows: normal rhythm, rate 85; low voltage of the QRS complexes; low T waves, slightly diphasic in Leads 1 and 2, having the appearance of digitalis effect; no abnormal axis deviation; P waves and PR intervals normal; normal R_4 and a rather low T_4.

During the six days in the hospital his many discomforts rapidly increased and his strength diminished. Chloral hydrate, Nembutal and Empirin Compound failed to give relief. A single dose of 1/6 gr. of morphine made him drowsy for twenty-four hours. Two abdominal paracenteses yielded less than a liter of fluid each. The specific gravity was 1.009. It contained 160 white cells (110 polymorphonuclears, 30 lymphocytes and 20 mono-

cytes) and 880 red cells per cubic millimeter. The sediment was negative for tumor cells.

On the sixth hospital night the house officer was called at 3:30 a.m. He found the patient dead, with large amounts of dark-red blood still oozing from the nose and mouth.

Differential Diagnosis

Dr. Alfred Kranes: It seems unlikely that the fall occurring nine months before death had much to do with this patient's illness, and I shall dismiss it from consideration, except to say that five weeks is a little long to be incapacitated from work because of a sprained knee and ankle. It raises the question whether some serious underlying disease was not already present, to which attention was directed by the fall. The appearance of the rash shortly thereafter is probably coincidental. Why a purpuric rash should itch puzzles me, for it has always been my impression that pruritus does not occur with purpura. Since clinical jaundice was noticed shortly thereafter, a possible explanation for the itching may have been the jaundice, rather than the rash to which it was attributed.

I regret that so little information is given concerning the first physical examination, which mentions only "probable ascites and an icteric tint to the scleras." Presumably the purpuric rash was present at that time. What would interest me more is a statement about the liver and spleen, since the former was easily felt on subsequent examination, and it would be important to know whether the apparent rapid increase in size was actually true. Since it is not mentioned, I am going to assume that the liver was not felt initially, and that it did rapidly increase in size, becoming tender in the process. The laboratory data, except for the slight rise in the icteric index, are normal at this examination.

The past history is of interest because of the attack of jaundice at twenty. Presumably this was catarrhal jaundice, which is the commonest type at this age and which may be related to his terminal illness, obviously involving the liver. Most cases of catarrhal jaundice clear up, leaving no residual liver damage, but a small percentage may either develop subacute yellow atrophy or show evidence of cirrhosis years later.

The problem is a very interesting one, and I am not at all sure that I can adequately explain it. The opening sentence of the history immediately suggests the possibility of some sort of heart disease, for which he was apparently treated with Salyrgan and digitalis. Furthermore it is implied that this resulted in lessening of the edema of his legs. Certainly the presence of an enlarged tender liver, ascites and edema of the legs is consistent with cardiac failure. However, I can find little in this story to support such a diagnosis. Although dyspnea is stated as one of his chief complaints, there is no further mention of it anywhere in the history. Furthermore there was no clinical evidence of pulmonary congestion, or of increased venous pressure except in the abdomen. If the large tender liver was due to cardiac failure, the neck veins should also have been distended. Nor did the examination of the heart itself show any evidence of disease, although the absence of enlargement clinically is not too reliable. The patient was probably too ill for x-ray examination. As for the electrocardiogram, all it reveals to me is a digitalis effect and the type of tracing one might expect in any debilitated patient without heart disease. I should like to ask Dr. Bland for his interpretation.

Dr. Edward F. Bland: We thought that there was no evidence of intrinsic disease of the cardiovascular system. The electrocardiogram was taken because of interest in the possible presence of heart disease secondary to the thoracic deformity.

Dr. Kranes: I think we can therefore safely dismiss heart disease from consideration. The past history, the presence of jaundice and ascites, evidence of collateral circulation in the abdominal wall, an easily palpable liver, the terminal hematemesis and the clinical effect of a small dose of morphine — al these factors are strong evidence in favor of some sort of intrinsic liver disease, probably cirrhosis, which I am inclined to believe was present. What type of cirrhosis is difficult to say without more history, but I favor a toxic cirrhosis despite the absence of known toxic factors. It would be of some interest to know whether he took any drugs such as cinchophen for relief of the pains in his legs following his fall, or whether he received injections of gold salts for what may have been diagnosed as an arthritis. Presumably not. There is no evidence that any arsenical drugs had been administered. The question of drug idiosyncrasy must be further emphasized because of the presence of the purpuric rash, which we have not explained, and to which I shall return in a moment. Despite the evidence in favor of cirrhosis there are a number of disturbing factors that argue against it.

In the first place his illness progressed much more rapidly than the usual case of cirrhosis, in the absence of any signs of subacute yellow atrophy. Furthermore, I cannot understand why the liver should have increased so rapidly in size, if that observation was correct. To be sure, estimates of liver size are likely to be quite erroneous, but this

was a comparative observation made at different times and is therefore likely to be somewhat more reliable. Then too, cirrhotic livers are not likely to be as tender as this one was. A tender liver is usually a congested one, or one that contains a malignant tumor. Also, the absence of splenomegaly is disturbing in a patient who has cirrhosis. Finally, I cannot see how a diagnosis of cirrhosis of the liver explains the most prominent clinical feature of his illness — the purpura. And I might add that I can find no other satisfactory explanation for it. A bleeding tendency does occur in severe liver disease with an increased prothrombin time; but I have never heard of its being confined so exclusively and so extensively to the skin, as in this case. The skin manifestations of a prolonged prothrombin time are likely to be diffusely ecchymotic rather than discretely purpuric. The fact that the purpura preceded by months the clinical evidence of liver disease need not disturb us, for I have seen patients admitted to the Emergency Ward with repeated epistaxes, only to turn up a year later with obvious cirrhosis. However, I find it difficult to believe that the purpura in this patient was in any way related to his liver disease.

I do not know what was the cause of the skin lesions. There is no evidence whatsoever pointing toward the usual causes of purpura, such as a primary blood dyscrasia and drug ingestion. The possibility of scurvy occurred to me in view of the perifollicular hemorrhages and the pains in the legs. Although he was extensively treated with vitamins A, B, D and K, there is no mention of his having received any vitamin C. Scurvy is an unusual disease these days, but even so it seems improbable that it was missed. Might I ask about his dietary history?

Dr. Bland: The patient had been on an adequate diet.

Dr. Kranes: That, I think, adequately disposes of the question of scurvy. Since I can find no satisfactory explanation for it, I shall have to call it purpura of undetermined etiology.

For the reasons that have already been stated, cirrhosis does not completely explain this picture, and it becomes necessary to consider whether any additional factors were present. The facts that the disease progressed fairly rapidly and that the liver increased in size while becoming tender immediately raise the question of cancer. If this patient had malignant disease I can see no way of making the diagnosis without further study, which was precluded because of his condition. Metastatic carcinoma could explain much of it, but without any anemia or obvious primary focus it remains only a possibility. Lymphoma of the liver is not only quite uncommon without other evidences of the disease, but a fever usually accompanies it, which was not present in this case. Another possibility is hepatoma, for which we seem to have the proper background — a pre-existing cirrhosis. Again one can only mention the possibility.

A rare possibility, which might be mentioned in an attempt to explain the rash, is acute disseminated lupus erythematosus, the skin lesions of which may be purpuric. It would explain the rash, the joint and abdominal pains, the ascites and the terminal renal failure without hypertension. However, it rarely occurs in men and, so far as I know, never involves the liver. We can therefore dismiss it. I do not believe there was any primary renal disease, despite the urinary findings and nitrogen retention. These can be attributed to the fact that there was terminal renal failure in an otherwise very ill patient.

In conclusion, my belief is that this patient had cirrhosis of the liver, but since this does not adequately explain the whole picture, I raise the question whether or not something else was present, such as a hepatoma.

Dr. Eugene R. Sullivan: Dr. Bland, you saw this case: would you care to add to the discussion?

Dr. Bland: It was extremely difficult to get an adequate history from this patient. In spite of the marked thoracic deformity of long standing we were convinced that the heart action was entirely competent. We agreed that cirrhosis of the liver was most likely; but the rather rapid progression in the size of the organ, its tenderness and the high degree of abdominal venous stasis developing in the course of a month suggested to us, as it has to Dr. Kranes, some additional complication, such as cancer.

I think it is important to emphasize the profound narcosis that a small dose of morphine produced in this patient. This in turn lent additional support to the diagnosis of extensive hepatic disease.

Dr. S. Peter Sarris: Should not hepatic-vein thrombosis be considered? That would explain the enlargement of the liver, apparently increasing under observation, and the fact that the patient failed more quickly than most of those with cirrhosis.

Dr. Kranes: In thinking over this problem I had considered that, but because of its rarity did not mention it. However, it is distinctly possible and would explain some of the atypical features.

Clinical Diagnoses

Cirrhosis of liver.
Subacute hepatitis.
Abdominal cancer?
Terminal hemorrhage, from esophageal or possibly gastric varices.

Dr. Kranes's Diagnoses

Cirrhosis of liver.
Hepatoma?
Purpura (? cause).

Anatomical Diagnoses

Primary liver-cell carcinoma (hepatoma), with extension into and obstruction of inferior vena cava.
Cirrhosis of liver, toxic.
Ascites.
Icterus, slight.
Gastric erosions, multiple, small, mucosal.
Duodenal ulcer.
Arteriosclerosis, moderate: aortic, coronary and peripheral.
Pulmonary tuberculosis, healed, localized: apical.
Kyphosis: thoracic.

Pathological Discussion

Dr. Tracy B. Mallory: I happened to prepare the clinical abstract of this case personally and, as I did so, amused myself by attempting to guess how it would be discussed. I expected that the discusser would briefly consider and quickly eliminate kyphoscoliotic heart disease. I then expected him to take up the confusing data regarding liver insufficiency — on the one hand, the low prothrombin value, the bromsulfalein retention and the terminal gastric hemorrhage, and on the other hand, the absence of demonstrable esophageal varices, of splenomegaly, of leukopenia, of lowering of the serum protein or of reversal of the albumin globulin ratio. I expected that he would reach the conclusion that cirrhosis of the liver alone could not explain the picture, and that he would advocate either malignant tumor or mechanical obstruction of the vena cava as the underlying factor. Dr. Kranes has reached the correct diagnosis by a slightly different route.

I should like to read two clinical notes from the hospital record, written before the patient died. The first is by Dr. Bland:

> My first impression is that the chief difficulties are portal obstruction and hepatic insufficiency of rather acute onset and probably complicating chronic asymptomatic liver disease. The normal serum protein and prothrombin determinations are disturbing.
>
> The thoracic deformity is a further handicap and has probably resulted in some strain on the right heart, but I am doubtful that cor pulmonale or inflow stasis to the heart is the important feature behind the jaundice, dermatitis, large liver, ascites and dilated veins below the diaphragm.
>
> I cannot feel the spleen; I hear no umbilical hum, and the heart on physical examination does not seem to be enlarged. The pulmonic second sound is not suspiciously loud, and there is no gallop. I cannot be certain of the cervical veins, but those on the dorsum of the hand seem slightly swollen above the level of the heart (? secondary to abdominal tension).

Dr. Chester M. Jones saw the patient in consultation and commented as follows:

> I cannot make a diagnosis. There is obvious embarrassment of the venous return through the vena cava. It is not possible to connect adequately the edema and the ascites with hepatic failure. If the ascites is purely mechanical and due only to intrahepatic disease, the absence of anemia, varices, splenomegaly and lowered serum albumin are unusual. I think that caval pressure must be considered and that carcinoma must be ruled out. Regardless of the underlying diagnosis, everything is exaggerated by his deformity. I believe he has an incurable disease and advise peritoneoscopy as the best means of establishing a diagnosis.

On post-mortem examination, we found a cirrhotic liver with a large nodule of hepatoma in the right lobe. This had spread, as it so often does, in the form of a tumor thrombus infiltrating along the hepatic venous radicles. A thrombus of tumor protruded from the main hepatic vein and was continuous with a similar mass that almost completely obstructed the inferior vena cava for its upper 7 or 8 cm. It stopped just short of the mouth of the cava at its junction with the right auricle. The cirrhosis was an old inactive one of the toxic type. The spleen was not enlarged, weighing only 170 gm., and there were no esophageal varices. The final hematemesis, which caused death, probably resulted in part from an extremely severe erosive gastritis with some fifty small, shallow, hemorrhagic erosions, mostly along the greater curvature, and in part from an acute duodenal ulcer about 2 cm. in diameter.

The heart was slightly enlarged but showed no evidence of cor pulmonale. The kidneys were large but showed only severe passive congestion, undoubtedly secondary to the caval obstruction. There was healed apical pulmonary tuberculosis, and one very large, densely calcified bronchial lymph node was found. There was nothing to explain the skin lesions, unless it was the liver disease.

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PASS THE AMMUNITION

We are reminded every so often that where there is no vision the people perish. Our vision has occasionally become very dim even if it has never entirely faded, and this has usually occurred when the present has seemed most fruitful and the future most promising. It is only when we are combating adversity that we realize the sweetness of its uses, and then, for a time, the veil is lifted from our eyes.

A year ago at Christmas time we had embarked on a common enterprise, each of us sharing the hopes of victory and risking the dangers of defeat. We were confused and uncertain then, fearful of our weaknesses and ignorant of our strength. We knew what we had been spared of the miseries of other peoples, but we did not know how long we might be spared them, or what else the future might contain. We knew only that a year of giving ground was in store for us—a year of sparring for time before we had strength to strike back.

Some of our weaknesses have been uncovered, and we know now that we have strength and courage and initiative in spite of the soft years that are behind us. We have put a girdle around the earth, if not, like Puck, in forty minutes; our youths are standing to their arms by Greenland's icy mountains and on Africa's golden sands. They are, to borrow further from the same literary source, basing their activities on the coral strands of India; and the heathen who, in his blindness has bowed down to wood and stone, bows also before the fire of our guns of destiny.

We are celebrating at this season the great pageant of Christianity, but it is as militant Christians that we are observing it. As we go forth to war, the Son of God goes with us. This year we will praise the Lord, as usual, but we will also pass the ammunition.

POLIOMYELITIS RESEARCH

During the last few years, much has been added to our scant understanding of an age-old disease, poliomyelitis. The virus, for example, has been isolated from the stools of patients and contacts and has been found both in sewage and in flies collected in epidemic areas. It is now thought, moreover, that the common portal of entry in man may be the alimentary tract, as well as, or perhaps in place of, the long-recognized route through the olfactory mucous membrane. A study of the transmission of the virus along axons and an evaluation of the various factors affecting its progress to the central nervous system are being actively prosecuted. The whole subject of neurotropic viruses and of their action on the body is, indeed, in the forefront of medical research today.

Not the least significant in this advance is the

work of Howe and Bodian.* They have shown that the virus of poliomyelitis is highly specific for the neuron and, in the peripheral nerves, migrates along the axons themselves rather than within the sheaths of the nerves. The rate of progress, according to their estimate, is 2 or 3 mm. per hour. Moreover, if the direct axonal pathway is not open, the virus may progress centrally through distant autonomic ganglions. How the virus penetrates the epithelium is still obscure, as is the problem why some intestinal contents tolerate the virus and some do not. In a rhesus (monkey), for example, the intestinal secretions are unfavorable for effective survival of the virus, whereas in a chimpanzee and in a cynomolgus (monkey), it is regularly found in the stools. These and other problems of host susceptibility are still matters for future research.

A most striking finding is their demonstration that susceptible nerve cells may become refractory during the time their injured axons are being reconstituted. The nature of this reaction is unknown, but it may depend on the chemical constitution of the cell protoplasm. The cells showing refractoriness to poliomyelitis still appear to be alive and capable of carrying on their normal functions. Such findings may well lead to changes in the treatment of the disease in human beings.

Other investigations by Howe and Bodian deal with the humoral mechanisms tending to protect the host at the portal of entry of the virus, the variability of susceptibility in different parts of the central nervous system, the local immunity of any one part afforded by a previous attack and the general problem of the control of poliomyelitis. On the last point, the following is quoted from the final paragraph of their summary:

> At the present time the control of poliomyelitis can be attempted along three lines, namely, preventing the virus from reaching the susceptible individual or, failing this, arresting the progress of the virus before it has reached the central nervous system or, lastly, limiting the spread of virus within the central nervous system. The development of these approaches is proceeding in a somewhat more satisfactory fashion with the acquisition of newer knowledge concerning the dissemination of virus, the portals of entry, and the forces which make for resistance in the organism. It seems not unlikely that the next few years will see more practical fruition of these efforts.

*Howe, H. A., and Bodian, D. *Neural Mechanisms in Poliomyelitis.* 234 pp. New York: The Commonwealth Fund, 1942.

OBITUARY

FRANCIS SEDGWICK WATSON†

1853 – 1942

It is the difficult duty of the writer of such a notice as this to try to give a word picture of a remarkably brilliant, handsome and versatile man, a character unique in the writer's experience, and most lovable. He was an excellent surgeon, a remarkable linguist, a most loyal friend, a faithful servant of the Boston City Hospital and the Harvard Medical School, a man of high ideals and fine sensibility. He was vibrant with the joy of life, and a most entertaining companion, a thorough sportsman and lover of the outdoors. Of his many summers spent on the Saguenay, he has left a most delightful account in that rare book, *A Bundle of Memories*, which it has been my privilege to read. In whatever he undertook, his ideals were of the highest. As one of his juniors on the staff of the Boston City Hospital I can give personal testimony to his kindness and helpfulness to the younger and less experienced members of the staff, to his readiness in encouragement and his frankness in criticism.

He was born in Milton, Massachusetts, on May 31, 1853, the son of Robert Sedgwick and Mary Hathaway Watson. He graduated from Harvard College in 1875, and from the Harvard Medical School in 1879. He was surgical intern at the Massachusetts General Hospital in 1878, his colleague being Dr. John B. Wheeler, that sterling surgeon of Burlington, Vermont, with whom he maintained a delightful and intimate friendship the whole of his long life. Their deaths came within a few months of each other.

The leading surgeons of the hospital at that time were Dr. Henry J. Bigelow, Dr. Richard M. Hodges, and Dr. C. B. Porter, all of whom he greatly admired, and of whom he has written delightfully in his *Bundle of Memories*. He had the greatest admiration for Dr. Bigelow, and being like him, a tall, handsome and brilliant man, with a very marked personality, he reminded his associates of that famous surgeon in his manner and ways of speaking, especially before the students. His real instinct for showmanship helped him to

†Read at the annual meeting of the Boston Surgical Society, Boston, December 7, 1942.

emphasize the points of his lectures and clinics, and his brilliant wit made them most entertaining.

After leaving the hospital, he studied in Europe for two years. Of these years he writes, "Those were glorious years, those years we passed in Europe, putting the finishing touches to our medical education, and while yet free from serious care and responsibilities." He studied at Vienna, after two months spent in a German family in Dresden in order to learn the language, and in Strasbourg he worked in the laboratories of Waldeyer and von Recklinghausen. On his vacations, he traveled extensively in Italy, Spain, France and North Africa. His description of his travels reveals a keen appreciation of the art, architecture, music and life in these countries as seen by a young, enthusiastic and brilliant observer. I do not know of any writing on travel more interesting and amusing than this part of his *Bundle of Memories.*

On his return to this country, he started practice in Boston, beginning by doing a dispensary district. He was surgeon for genitourinary diseases at the Boston Dispensary, and surgeon to out-patients at the Children's, Boston City and Carney hospitals. He was instructor and lecturer on minor surgery and genitourinary diseases at the Harvard Medical School. In 1894, he became visiting surgeon at the Boston City Hospital, and in 1896 was the head of the Genitourinary Department at Harvard, and was president of the American Society of Genito-Urinary Surgeons, presiding at the triennial meeting in Washington. In 1890, he had been a delegate from the American Association of Andrology to the International Medical Association in Berlin. In 1897, he was invited by the Russian Committee of the International Medical Congress, which met in Moscow, to be one of the honorary presidents of the Congress of the Society of Surgery. He attended the meeting, and astonished and delighted the natives by giving his address in Russian, which, needless to say, was a result of much study and a *tour de force* of memory. Of this he writes:

> The president called on me to speak and I began in French, saying that I would very much like to respond to our hosts in their own language, and that if they would be indulgent, I would make the attempt to do so. Then I sailed in. With the first words a low murmur arose from the Russians. I at once felt that I had placed the accent on the wrong syllable somewhere in the phrase, and broke into a cold perspiration as the vision of the long journey to Siberia, which was called into being by my heated imagination, arose before me. I felt persuaded that I must have said "to hell with the Tsar," or some equally damning words, and braced myself to meet the worst. Then I noticed that the Russians were advancing toward me, holding their champagne glasses in their hands, and smiling encouragement. Being thus relieved as to my fate, I went on with the following few words.

These few words proved to be a delightful message of thanks to the Russians for their warm hospitality, and a statement of the pleasant memories he should carry home, and wishes for their good fortune, happiness and success. The enthusiasm of the Russians for his address passed all bounds, and, therefore, many healths were drunk, and he had to pretend to drink them in order to avoid direful consequences.

In 1908 with Dr. John H. Cunningham, Jr., he published a complete textbook on diseases of the genitourinary system, which has remained a standard treatise to this day.

Besides the local and national societies, he was a member of the International Surgical Society, the Urological Society of Germany and that of Russia, a corresponding member of the Surgical Society of Moscow and an active member of L'Association Française d'Urologie (vice-president in 1911). In 1921 he was elected honorary president of Societé Internationale d'Urologie.

In 1906, he resigned as surgeon-in-chief at the Boston City Hospital and lecturer at the Harvard Medical School after twenty-five and thirty years, respectively, of service. He was a charter member of the Tavern Club, and contributed a brilliant play which he wrote and staged among many other contributions to its proceedings.

He was married at Boston, June 16, 1886, to Mary Perkins, who died at Boston, September 19, 1917. In October, 1918, he married Genevieve Walker. He had one daughter, who died in infancy, by his first marriage.

In his surgery, he was forward-looking and courageous. He lived through the time when prostatectomy became a recognized operation, and did much, by example and writing, to help on the adoption of this operation, which has been so great a boon to many sufferers.

In 1888, Dr. Watson presented in monograph, the first classification of the gross pathology of the prostate and formulated the proper surgical procedures to deal with the various types. He emphasized the advantage of attack of certain intravesical growths suprapubically and smaller hypertrophies, both sclerotic and malignant, through the perineum. These principles remain the same today, and it is generally recognized that it was his foresight that outlined the surgical principles now employed.

He was also a pioneer in the electrical destruction of tumors of the bladder, for which he invented an instrument to be employed through suprapubic exposure, as well as the destruction of prostatic hypertrophy with a galvanocautery instrument of his own invention, which was employed by intraurethral manipulation, a procedure that antedated those of Friedenburg and Bottini.

In the New England Surgical Society, who of the members can forget his brilliant addresses at two meetings, in Portland, Maine, and St. Albans, Vermont, where his wit flashed like a comet across the level of our scientific monotony? The dinner at Vermont was held on one of the Lake Champlain steamers, and the combination of the good dinner, the lovely lake and Frank Watson's address cannot soon be forgotten.

I cannot close this notice of a beloved, loyal and brilliant friend without saying a word about his admiration and appreciation of his older friends and colleagues, such as Drs. David Cheever, Ned Bradford and George W. Gay, of whom he wrote most charmingly in his *Memories*. Loyalty and kindness were his chief characteristics, and there was not a mean, jealous or unkind drop of blood in his body. He differed from most of us in his facility and clearness in the expression of his thoughts and feelings, and these thoughts and feelings to the last were those of a good friend and gallant gentleman.

F. B. L.

MEDICAL EPONYM

Skodaic Tympany

This is described by Dr. Joseph Skoda (1805-1881), chief physician of the Vienna General Hospital, in his book, *Abhandlung über Perkussion und Auskultation* [*Treatise on Percussion and Auscultation*] (Vienna, 1839). A portion of the translation from the third edition (Vienna, 1844) follows:

> It would seem contrary to the laws of physics that a lung containing a small amount of air should give a tympanitic note, whereas the same lung with an increased air content is not tympanitic. The fact, however, is well established and is borne out not only by experiments made on the cadaver, which will be referred to later, but by the constant finding that in the presence of exudate in the thoracic cavity, which entirely compresses the lower part of the lung and markedly reduces the volume of the upper lobe, the percussion note is distinctly tympanitic over the upper part of the thorax.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

SECRETARY'S OFFICE

Dr. Frank H. Lahey, chairman of the Directing Board of the Procurement and Assignment Service, has requested the publication of the following statement, dated December 16.

Michael A. Tighe, *Secretary*

* * *

It is of the utmost importance that the Procurement and Assignment Service for Physicians, Dentists and Veterinarians, immediately has the name of any doctor who really is willing to be dislocated for service, either in industry or in overpopulated areas, and who has not been declared essential to his present locality. This is necessary if the medical profession is to be able to meet these needs adequately and promptly. We urgently request that any physician over the age of forty-five who wishes to participate in the war effort send in his name to the state chairman for the Procurement and Assignment Service in his state.

COMMITTEE ON MATERNAL WELFARE

Analysis of Causes of Maternal Death in Massachusetts during 1941

Toxemia and Eclampsia (*Concluded*)

Of the remaining 19 cases of toxemia and eclampsia, 6 patients died undelivered and 13 were delivered normally or by vaginal operation.

The first of the 6 undelivered patients was a woman in her second pregnancy on whom a diagnosis of essential hypertension had been made before pregnancy, since her systolic blood pressure consistently ranged from 160 to 180. Following an attack of abdominal pain the blood pressure rose to 290 systolic, 140 diastolic and she was sent immediately to the hospital. After a convulsion she went into coma and died undelivered. Autopsy revealed scattered hemorrhages throughout the viscera, cerebral hemorrhage and acute peripheral necrosis of the liver. This patient should not have been allowed to become pregnant.

The second patient, a multipara who had had no prenatal care, was known to have chronic hypertension. She was not seen until the seventh month, at which time she had a convulsion. She was immediately hospitalized, being comatose on arrival, and died undelivered. It is probable that

this patient should not have been allowed to become pregnant; however, intelligent prenatal care might have averted this disaster. Cerebral hemorrhage was probably the immediate cause of death.

The third case was that of a patient who had not seen a physician throughout her pregnancy, was seized with convulsions when at term and was hospitalized. She was unconscious on entry; the blood pressure was 186 systolic, 114 diastolic, there was albumin in the urine, and the fetal heart was inaudible. The patient died undelivered. Fortunately an autopsy was performed, which revealed eclampsia and acute passive congestion of the kidneys. This was probably an unnecessary death. It is shocking that no medical advice was sought or given during pregnancy until eclampsia itself was present.

The fourth patient, a primipara who had had no prenatal care, was admitted to the hospital in active convulsions, which were followed by coma. Conservative treatment alone was employed; death occurred twenty-four hours after admission. The patient was undelivered, but a stillborn fetus was obtained by post-mortem cesarean section. Autopsy showed focal necrosis of the liver, fatty degeneration of the heart and cardiac dilatation. There is little to be said about this case. Present-day knowledge would lead one to suppose that intelligent and adequate prenatal care would have averted this catastrophe. Certainly eclamptic symptoms existed a few weeks before the convulsions occurred and, if recognized, might have responded to treatment directed toward the removal of the fetus before the eclamptic seizures occurred.

The fifth patient was a primipara who had a normal pregnancy until she reached the twenty-second week, at which time she was "taken ill" while at the beach and advised to return to her own home. Shortly after reaching home she had a convulsion and was seen by her physician, who found a blood pressure of 200 systolic, 140 diastolic, considerable edema and a large trace of albumin in the urine. She was immediately sent to the hospital, where labor started spontaneously the day after entry, but went steadily downhill and died undelivered. This was a very early case of eclampsia. It is possible, although the history does not suggest it, that some chronic kidney involvement was behind this. No attempt to operate was made, and from this standpoint the treatment can in no way be criticized.

The history of the sixth patient is inadequate. At eight and a half months she apparently developed acute eclampsia, and the baby was not delivered. Autopsy revealed fulminating toxemia and central necrosis of the liver.

The 13 remaining patients were delivered normally or by vaginal operation. The first patient was a twenty-three-year-old primipara who had had a nephrectomy several years previously and who, at eight and a half months, had a blood pressure of 160 systolic, 100 diastolic, and a large trace of albumin in the urine. She was hospitalized, and an attempt at induction of labor by packing the cervix was unsuccessful. The vagina, however, was packed with gauze the following day, and labor was initiated. The next day she had a convulsion, at which time she was said to be fully dilated. Delivery was accomplished by forceps, but the patient continued to have convulsions and died thirty-six hours post partum. It is possible that delivery should have been considered sooner; furthermore, the practice of packing of the cervix to induce labor is antiquated. The existence of only one kidney was undoubtedly contributory to the toxemia that resulted fatally.

The second patient, whose first baby had been delivered by cesarean section, had had inadequate prenatal care. On the twenty-first week she was presumably all right, but on her next visit, five weeks later, she had an increased blood pressure with albuminuria and edema. She was immediately hospitalized, but conservative treatment did not achieve any benefit. The patient went into convulsions; labor, which was normal, was induced by rupture of the membranes and was followed by delivery of a macerated fetus. The patient did not regain consciousness and died shortly after delivery. The treatment in this case cannot be criticized. The patient herself was at least partly to blame for not making regular prenatal visits.

The third patient, a thirty-six-year-old primipara on whom a diagnosis of essential hypertension had previously been made, did not consult her physician until approximately six months pregnant, at which time she had a systolic blood pressure of 260, a urine filled with casts and a ++++ test for albumin. Instead of being immediately hospitalized, she was sent home to bed. Two weeks later she was sent to the hospital. Labor began spontaneously the day after entry, and she delivered herself of a macerated fetus. She apparently had a convulsion during delivery, which resulted in a cerebral hemorrhage; she did not recover consciousness and died a few hours later. It is questionable whether this patient should have ever been allowed to become pregnant, and in the event of pregnancy, abortion should have been advised at her first prenatal visit. She should have been hospitalized when first seen; and an early delivery when the symptoms did not abate might have prevented this fatality.

The fourth patient was a woman in her second pregnancy who was given adequate prenatal care from the beginning of pregnancy; she was classified as having a Grade I pre-eclampsia. Before delivery the blood pressure was 160 systolic, 98 diastolic. She went to term and was delivered normally, convalescence being uneventful until the thirteenth post-partum day, when she had convulsions, which were followed by a cerebral hemorrhage. Death occurred three days later, and autopsy revealed cerebral thrombosis and hemorrhage and chronic rheumatic heart disease; there was no reference to pathologic lesions of the kidneys. In no way can the handling of this case be criticized.

The fifth patient was a primipara who, at eight and a half months, had definite toxemia associated with separation of the placenta. A normal delivery was followed by two convulsions two days afterward, from which the patient did not recover. There was absolute suppression of urine post partum. The treatment of anuria associated with toxic separation of the placenta by decapsulation of the kidney has often proved successful, and its use might have done some good in this case.

The sixth patient was a multipara who was seen only once during her pregnancy, when just short of seven months. Ten days afterward she had a cold, with a temperature of 104°F. Labor started spontaneously the following day, and a premature infant was delivered. That evening the patient became desperately ill and was sent to the hospital, where she died shortly after entry. Autopsy revealed toxemia of pregnancy. This history is so sketchy that it is difficult to make the information given to the investigator correlate with the facts. The autopsy, however, showed that toxemia was the real cause of this fatality, although the attending physician made no mention of increased blood pressure or albuminuria. This patient had neither adequate prenatal care nor intelligent care after she had seen her physician.

The seventh patient, a primipara who was said to have a large trace of albumin and a systolic blood pressure of 140 at five months, was not seen again for two weeks, at which time the physician was summoned to her home and found her complaining of headache and blindness, with a systolic blood pressure of 200 and a urine solid with albumin. The following day she delivered herself spontaneously of a stillborn infant. Acute anuria developed, and death occurred six days afterward. This patient was not given intelligent or hardly humane treatment.

The eighth case was that of a primipara who was known to have had hypertension and albuminuria and who had had excellent prenatal care. The only criticism of the case is that the patient was allowed to go into spontaneous labor at term with a systolic blood pressure of 200 and without being hospitalized before delivery. Convulsive seizures occurred after delivery, and the patient died of anuria fifteen days post partum. This is a case of post-partum eclampsia that undoubtedly was the result of hypertensive kidneys. Had this patient been delivered at eight months, when the baby was viable, the fatality in all probability would not have occurred.

The ninth case was that of a patient who had been toxic during pregnancy two years previously and had been delivered of a stillborn infant. She was not seen until the seventh month of her second pregnancy, at which time she was said to have been normal. When near term she became irrational and the systolic blood pressure rose to 160, with marked edema and moderate albuminuria. The toxemia was accompanied by jaundice. Six hours after the induction of labor by artificial rupture of the membranes a stillborn fetus was delivered, and the patient expired shortly after delivery from circulatory collapse, which may well have been due to the toxic myocarditis that is occasionally associated with severe toxemia. The jaundice suggests liver involvement. This patient was not given adequate prenatal care, especially in view of her previous toxemia.

The tenth patient, a primipara who had had no prenatal care, gave an entirely negative history up to the time of labor, which started prematurely at six and a half months; she was sent to the hospital, and delivery was accomplished soon after entry. A convulsion occurred immediately after delivery, and anuria was followed by death one week later. Intelligent prenatal care would have undoubtedly averted this disaster.

The eleventh patient was a primipara who had had moderately intelligent prenatal care and was said to have been normal until the end of the seventh month, when the blood pressure was 160 systolic, 100 diastolic. One week later the blood pressure returned to normal, but three weeks before the onset of labor it again became elevated. The patient was not seen again until she had a convulsion, at which time the blood pressure was 190 systolic, 120 diastolic. A stillborn child was delivered not long after hospital entry. Anuria developed immediately after delivery. Probably a cerebral hemorrhage was the immediate cause of death, which occurred twelve hours after delivery. Of course, this patient should have been seen more frequently at the end of pregnancy. It is difficult to understand how any physician could let three weeks go by without seeing a patient whose systolic blood pressure was 190.

The twelfth patient, a primipara who had had adequate prenatal care, was sent to the hospital at the beginning of the tenth month because of a systolic blood pressure elevated to 180, edema and considerable albuminuria. The day after entry she had two convulsions; labor started spontaneously, and a stillborn infant was delivered by low forceps. The patient was comatose after delivery and died twelve hours later. Autopsy was performed, but unfortunately the report could not be found. In this case, delivery should have been considered earlier.

The history of the thirteenth and final case is inadequate; apparently toxemia proved fatal in a patient who was delivered normally at term.

In the entire series of 27 cases, six autopsies were performed.

In reviewing these cases of toxemia and eclampsia, it is extremely gratifying to find that in none was *accouchement forcé* resorted to. In only one case can the operative management be criticized, this being the one in which cervical packing was attempted. It is deplorable that so many of these cases were treated by cesarean section after eclampsia had established itself, since it is almost an axiom that an eclamptic seizure contraindicates section. It is also deplorable that some of these patients with eclampsia had no prenatal care, and one cannot help but believe that some of them at least might have been saved had they been seen routinely during pregnancy. The number of patients who died undelivered is noteworthy. Eclampsia may certainly be a rapidly fatal disease.

The two patients on whom nephrectomy had been performed years previously illustrate the potential seriousness of pregnancy in a patient with one kidney. Such patients should be watched more carefully than the normal pregnant woman, and it might be well, for the purpose of saving added work on the one remaining kidney, to anticipate labor by the proper method of emptying the uterus after viability.

The tabulation for 1941 shows an increase of 2 in the deaths from toxemia and eclampsia as compared with that for 1940. An analysis of these deaths in 1941 clearly shows that many of them were preventable.

A CORRECTION

I wish to correct a statement made in the report to the Council of the Massachusetts Medical Society of my survey of the state-aided cancer clinics, which appeared in the November 12 issue of the *Journal*.

When I visited the clinic at the Boston Dispensary I was told they did not have facilities for treatment with a high-voltage x-ray machine. Mr. Frank E. Wing, the director, now tells me I was misinformed and that a 200,000-volt machine for patients requiring that form of treatment was installed several years ago.

CHANNING C. SIMMONS, M.D.

DEATHS

BRIGGS — CHARLES A. BRIGGS, M.D., of Assonet, died December 14. He was in his eightieth year.

Dr. Briggs received his degree from the Long Island College of Medicine in 1889. He was appointed school physician soon after he went to Assonet to practice. He was a fellow of the Massachusetts Medical Society and the American Medical Association.

His widow and a daughter survive him.

DIXON — ROBERT B. DIXON, M.D., of Boston, died December 16. He was in his eighty-seventh year.

Born in Damariscotta, Maine, he received his degree from Harvard Medical School in 1879. For twelve years he was physician at the Boston Dispensary and was commissioner on the Massachusetts Nautical Training School. He had been a director of the Robert B. Brigham Hospital since it was founded. He was a fellow of the Massachusetts Medical Society and the American Medical Association. For a number of years he was associated with the Medical Department of the Employers Liability Assurance Corporation.

Three daughters and five grandchildren survive him.

OLEF — ISADORE OLEF, M.D., of Dorchester, died December 16. He was in his forty-sixth year.

Dr. Olef received his degree from Harvard Medical School in 1926 and at the time of his death was assistant professor of medicine at Tufts College Medical School. He was a fellow of the Massachusetts Medical Society and the American Medical Association.

His widow and two daughters survive him.

WAR ACTIVITIES

CIVILIAN DEFENSE

LESSONS FROM BRITISH EXPERIENCE IN CIVIL DEFENSE

The following circular (Medical Series No. 20) was recently sent to all regional directors and regional medical officers by Dr. George H. Baehr, chief medical officer, United States Office of Civilian Defense:

Three years of British experience with air raids have significantly modified earlier concepts regarding the field casualty services. The following observations made on a recent inspection of emergency medical facilities in England and Scotland are forwarded for your information and for transmission through state chiefs to local chiefs of Emergency Medical Services.

(1) Heavy raids occur invariably at night; heavier high-explosive bombs and land mines are now being employed, up to 2000 kg., with much greater destructive ef-

fects. Incendiary bombs are used in much larger numbers, and fire is now the most serious hazard. Daylight raids are usually hit-and-run affairs in which solitary planes participate.

(2) In large cities the field casualty services may handle 2500 to 3500 casualties during a night raid. All serious casualties are moved directly to hospitals, never to first-aid posts. Heavy raids are apt to be repeated on subsequent nights when the protective forces are exhausted.

(3) A large fleet of four-stretcher ambulances is essential for life saving. Fourteen thousand ambulances were made in England and Scotland by purchasing used cars, stripping them and then mounting a simple ambulance body on the chassis. London uses over 1500 such ambulances and 550 sitting-case cars. The use of tradesmen's trucks proved universally unsatisfactory; three out of four never arrived on the scene, and lives were lost owing to the delay and confusion. Because of the large number of casualties to be transported in a few hours, no ambulances that carry less than four stretchers are employed. For the simultaneous evacuation of damaged hospitals, a fleet of 200 converted buses carrying 10 stretcher cases and 6 to 10 sitting cases are immediately available, and another 200 are obtainable within two hours.

(4) Casualty stations (British fixed first-aid posts) are necessary at or near all hospitals and at places more than a mile from hospitals to care for minor casualties that do not require hospitalization. Many are now on a care-and-maintenance basis and are activated only during a raid. When functioning, the staff usually consists of one or two doctors, several nurses and a variable number of aides and auxiliaries.

(5) In large cities, casualty stations need not be more numerous than one per 25,000 inhabitants; they should be located about a mile apart. There are less than 300 in the London area, with a population of about 10,000,000 and a land area more than twice that of Greater New York. In smaller, thinly settled communities, they are more numerous in relation to population, but the distances between them are proportionately greater than in metropolitan cities. Many of the minor casualties are moved to first-aid posts in sitting-case cars; some walk.

(6) First-aid parties (stretcher teams) are not necessary, are a waste of manpower and are rapidly being eliminated. First aid at incidents is essentially a function of the rescue parties (rescue teams), which extricate the casualties from under the debris of demolished buildings. All first-aid parties in England and Scotland are therefore being merged into the rescue parties. They include a leader, an assistant leader and eight other members, and are entirely independent of the fire department. They are a life-saving service related to the medical services concerned in field casualty work.

(7) The experiences of Britain under air-raid conditions have dispelled many preconceived notions concerning first aid. Almost all raids occur at night; the victims are crushed under the debris of demolished buildings and are either dead or severely injured; less than a third are slightly injured and can be cared for at casualty stations; all the severely injured must go to a hospital; victims are invariably covered with dust and dirt, which hangs in the air for hours. The conditions under which the rescue workers encounter the injured beneath the structural debris, the darkness, and the dust that always fills the air, the large proportion of dead and severely injured, and the urgent need for immediate hospitalization make it impossible to apply most peace-time concepts of first aid.

(8) Wounds are usually grossly contaminated and need only be covered with a shell dressing until the casualty reaches the hospital. Hemorrhage is usually controllable with a pressure dressing. The tourniquet is rarely employed. Burns are covered only with sterile gauze until the casualty arrives at the hospital. Tannic-acid jelly as a first-aid dressing for burns has been discarded because of the dirt that invariably contaminates the burned surface, because the jelly deteriorates rapidly and, lastly, because tannic acid ignites in the presence of phosphorus when applied to burns caused by the explosion of phosphorus-oil bombs.

(9) Traction splints are not used. An exception is made if the casualty must be transported a long distance over country roads. Unlike Army field experience in the last war, the few miles of travel to a hospital over the paved roads of a city do not warrant the application of traction, especially as the darkness and the conditions of an air raid also make hurried application of the procedure difficult or impossible. All that can be done is to place the fractured extremity gently in alignment, bind it with triangular bandages to the uninjured leg or to an improvised splint, or apply a Thomas splint if one is on hand. Movement of the fragments can also be minimized by snug application of the blankets according to the Wanstead technic of blanketing and by the use of sandbags, which should always be carried in the ambulance.

(10) Shock is treated at the incident by prompt administration of adequate doses of morphine (up to ½ gr. for adults), coramine, proper blanketing, administration of fluids, and the use of hot-water bottles during transportation to the hospital. The use of plasma or blood transfusion is deferred until arrival at the hospital; it is ordinarily quite impossible in the darkness, dirt and confusion at the incident.

(11) The presence of a physician at the incident is invaluable, but more than one is unnecessary. In fact, one physician may cover several nearby incidents, leaving his nurse or one of the nursing auxiliaries of his emergency team at the incident while he moves temporarily from one to another in the immediate neighborhood.

(12) Even though a single night's casualties requiring hospitalization may total 1000 or 2000, large hospitals rarely receive more than 50 to 100, the load being distributed as evenly as possible throughout the city.

(13) A large casualty receiving hospital is often related to one or more peripheral hospitals in the suburbs or in a country district. There are now four base-hospital beds for each casualty bed in the cities.

(14) On receipt at a local report and control center of a message from an air-raid warden that an incident and casualties have occurred, an "express party" is immediately dispatched to the scene. An "express party" includes one rescue first-aid party, one ambulance, one sitting-case car, and one mobile medical unit (mobile medical team). The latter consists of one physician, one nurse and two auxiliaries. No other equipment and personnel of the emergency medical service is dispatched unless additional assistance is requested by the incident officer (usually a higher police official) or by the incident physician on the scene. In this manner, useless movement is avoided and equipment and personnel of the community is carefully conserved.

NOTICES

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING SUNDAY, DECEMBER 27

WEDNESDAY, DECEMBER 30

*12:00 m. Clinicopathological conference. Children's Hospital.

*Open to the medical profession.

FEBRUARY 13. American Board of Obstetrics and Gynecology. Page 690, issue of October 29.

MAY 18, 19. Massachusetts Medical Society. Springfield.

DISTRICT SOCIETIES

BRISTOL SOUTH
MAY 6. New Bedford.

ESSEX NORTH
JANUARY 6.
MAY 5.

ESSEX SOUTH
JANUARY 6. Danvers State Hospital.
FEBRUARY 3. Lynn Hospital.
MARCH 3. Essex Sanatorium.
APRIL 7. Addison Gilbert Hospital, Gloucester.
MAY 5. Salem Country Club.

FRANKLIN
JANUARY 12.
MARCH 9.
MAY 11. Annual meeting.

All meetings are held at 11:00 a.m. at the Franklin County Hospital, Greenfield.

HAMPSHIRE
JANUARY 6.
MARCH 3.
MAY 5.

MIDDLESEX EAST
JANUARY 27.
MARCH 17.
MAY 5.

All meetings are held at the Bear Hill Golf Club, Stoneham, at 12:15 p.m., except that of May 5, which will be held at 6:30 p.m.

MIDDLESEX NORTH
JANUARY 27.
APRIL 28.
JULY 28.

PLYMOUTH
JANUARY 21. Brockton Hospital.
FEBRUARY 18. Jordan Hospital, Plymouth.
MARCH 18. Goddard Hospital.
APRIL 15. Bridgewater State Farm.
MAY 20. Lakeville.

WORCESTER
JANUARY 13. St. Vincent Hospital, Worcester.
FEBRUARY 10. Worcester State Hospital, Worcester.
MARCH 10. Memorial Hospital, Worcester.
APRIL 14. Hahnemann Hospital, Worcester.
MAY 12. Annual meeting.

WORCESTER NORTH
JANUARY 27.
APRIL 28.
JULY 28.

~~(Books Received on page ix)~~

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